Report on the Deliberation Results

September 1, 2022

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate (JAN*)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2021

Results of Deliberation

In its meeting held on August 29, 2022, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Given the extremely limited number of Japanese patients participated in clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data are gathered from a certain number of patients to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

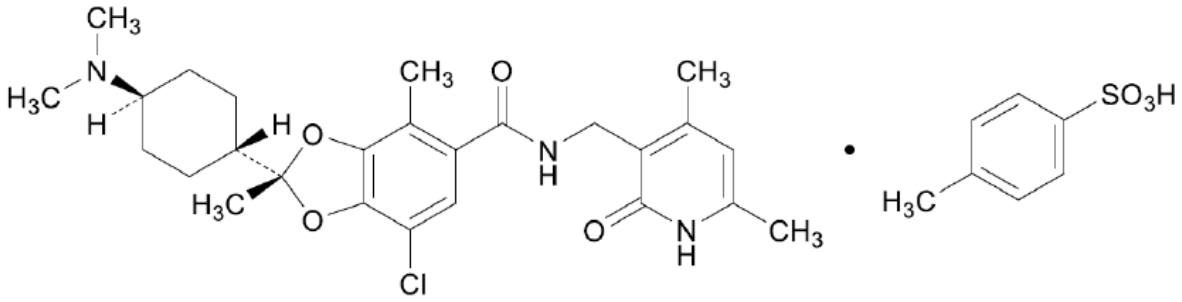
Review Report

August 8, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2021
Dosage Form/Strength	Tablets: Each tablet contains 67.6 mg or 135 mg of Valemetostat Tosilate (50 mg or 100 mg of valemetostat).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{26}H_{34}ClN_3O_4 \bullet C_7H_8O_3S$

Molecular weight: 660.22

Chemical name: (2R)-7-Chloro-2-[*trans*-4-(dimethylamino)cyclohexyl]-*N*-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2,4-dimethyl-1,3-benzodioxole-5-carboxamide mono(4-methylbenzenesulfonate)

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 526 of 2021 [*R3 yaku*]; PSEHB/PED Notification No. 1122-1 dated November 22, 2021, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with relapsed or refractory adult T-cell leukemia-lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Myelosuppression, infections, and secondary malignant tumor are subject to further investigation through post-marketing surveillance.

Indication

Relapsed or refractory adult T-cell leukemia-lymphoma

Dosage and Administration

The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Given the extremely limited number of Japanese patients participated in clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data are gathered from a certain number of patients to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

June 24, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2021
Dosage Form/Strength	Tablets: Each tablet contains 67.6 mg or 135 mg of Valemetostat Tosilate (50 mg or 100 mg of valemetostat).
Proposed Indication	Relapsed or refractory adult T-cell leukemia-lymphoma
Proposed Dosage and Administration	The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Enhancer of zeste homolog 1 and 2 (EZH1/2) are components of polycomb-repressive complex 2 (PRC2) that modulates gene expression through histone modification. By catalyzing the attachment of methyl groups to the lysine residues of proteins such as histone (methylation), EZH1/2 are thought to mediate chromatin condensation and repress gene transcription, etc., thereby being involved in T-cell differentiation and proliferation (*Mol Cell.* 2008;32:503-18).

Valemetostat Tosilate (hereinafter referred to as "valemetostat") is a low-molecular compound with inhibitory effect against EZH1/2 discovered by the applicant. Valemetostat is expected to suppress tumor growth by inhibiting the methylation activity of EZH1/2 and inducing apoptosis, etc.

1.2 Development history, etc.

The applicant initiated a global phase I study (Study DS3201-A-J101 [Study J101]) in patients with relapsed or refractory non-Hodgkin lymphoma (NHL) in March 2016.

As of May 2022, valemetostat has not been approved for the indication of relapsed or refractory adult T-cell leukemia-lymphoma (ATLL) in any country or region.

In Japan, the applicant started patient enrollment in the Study J101 in [redacted] 20[redacted]. Then, the applicant initiated a Japanese phase II study in patients with relapsed or refractory ATLL (Study DS3201-A-J201 [Study J201]) in November 2019.

Recently, an application for valemetostat has been submitted with the results of Study J201 as pivotal data.

Valemetostat was designated as an orphan drug with the intended indication of "relapsed or refractory adult T-cell leukemia-lymphoma" in November 2021 (Orphan Drug Designation No. 526 of 2021 [*R3 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale yellow-white powder. The general properties, including description, solubility, hygroscopicity, melting point, acid dissociation constant, and distribution coefficient were determined. At least 6 types of [redacted] were identified in the drug substance, but data demonstrated that the commercial manufacturing process produces only [redacted] and the stability testing confirmed that [redacted] remains unchanged .

The chemical structure of the drug substance was elucidated by elemental analysis, mass spectrometry, ultraviolet-visible spectroscopy (UV/VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR).

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] as starting materials.

The quality control strategy was constructed by the following investigations (Table 1).

- Identification of critical quality attributes (CQAs)
- Identification of material attributes with a potential impact on product CQAs and investigation on acceptable ranges of manufacturing process parameters based on quality risk assessment, etc.

Table 1. Outline of control strategy of drug substance

CQA	Control method
Identification	Specifications
Content	Specifications
Related substances [redacted]	[redacted], specifications
[redacted]	[redacted]
Residual solvents	[redacted], specifications
[redacted]	[redacted]
[redacted]	Specifications

Critical steps include the [redacted] of [redacted] and the [redacted] of [redacted]. As critical intermediates, [redacted] and [redacted] are controlled.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR), purity (related substances [high-performance liquid chromatography (HPLC)] and residual solvents [gas chromatography (GC)]), residue on ignition, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows main stability studies conducted on the drug substance. The results indicate favorable stability. The photostability testing demonstrated that the drug substance is stable to light.

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot scale batches	25°C	60%RH	[redacted] low density polyethylene bag + polyethylene drum	24 months
Accelerated		40°C	75%RH		6 months

Based on the above, a retest period of 36 months was proposed for the drug substance when stored at room temperature in [redacted] low density polyethylene bags and placed in polyethylene drums, in accordance with the Guideline on Evaluation of Stability Data (ICH Q1E guidelines). Long-term testing will be continued up to 60 months.

[redacted]

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 67.6 mg or 135 mg of the drug substance (50 mg or 100 mg of valemetostat). The drug product contains microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, light anhydrous silicic acid, magnesium stearate, hypromellose, talc, titanium oxide, yellow ferric oxide (100-mg tablets only), and red ferric oxide (100-mg tablets only) as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of blending 1, granulation, blending 2, tableting, coating, and packaging. [redacted] is defined as critical step, and process control is specified in [redacted].

The quality control strategy was constructed by the following investigations (Table 3).

- Identification of CQAs
- Identification of material attributes with a potential impact on product CQAs and investigation on acceptable ranges of manufacturing process parameters based on quality risk assessment, etc.

Table 3. Outline of control strategy of drug product

CQA	Control method
Description	Specifications
Identification	Specifications
Strength	[redacted], specifications
Uniformity of dosage units	[redacted], specifications
Dissolution	[redacted], specifications
Purity (related substances)	[redacted]
Stability	[redacted], specifications
[redacted]	

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC and UV/VIS), uniformity of dosage units (content uniformity [HPLC]), dissolution (UV/VIS), and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows main stability studies conducted on the drug product, and the results indicate favorable stability. The photostability testing demonstrated that the drug product is stable to light.

Table 4. Stability studies of drug product

Strength	Study	Primary batches	Temperature	Humidity	Storage form	Storage period
50 mg	Long-term	2 commercial scale batches 1 small-scale batch	25°C	60%RH	Blister pack ([redacted]/aluminum) + desiccant + pillow package ([redacted])	12 months
	Accelerated		40°C	75%RH		6 months
100 mg	Long-term	2 commercial scale batches 1 small-scale batch	25°C	60%RH		12 months
	Accelerated		40°C	75%RH		6 months

Based on the above, a shelf life of 24 months has been proposed for the drug product when stored at room temperature in a blister pack ([redacted]/aluminum), which is filled in a pillow package with [redacted] using silica gel as a desiccant, in accordance with the ICH Q1E guidelines. Long-term testing will be continued up to 36 months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and drug product has been appropriately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In this section, doses and concentrations of valemetostat are expressed as amounts of the free base.

3.1 Primary pharmacodynamics

3.1.1 Inhibition against histone methylation

3.1.1.1 *In vitro* (CTD 4.2.1.1-1 and 4.2.1.1-3)

The inhibitory effect of valemetostat against histone methylation by human PRC2[7)] (recombinant protein) comprising EZH1 or EZH2 was investigated by determining an amount of the radiolabeled methyl group enzymatically transferred. The 50% inhibitory concentration (IC_{50}) of valemetostat against PRC2 comprising EZH1 or EZH2 was 10 or 6.0 nmol/L (n = 1), respectively.

The inhibitory effect of valemetostat against histone H3 lysin 27 (H3K27) trimethylation was investigated using human colorectal cancer HCT116 cell line expressing wild-type EZH1/2 by luminescent oxygen channeling immunoassay (LOCI). IC_{50} of valemetostat was 0.55 nmol/L (n = 1).

3.1.2 Growth inhibitory effect against hematopoietic malignancy cell lines

3.1.2.1 *In vitro* (CTD 4.2.1.1-5)

The growth inhibitory effect of valemetostat against 4 human hematopoietic malignancy cell lines was investigated using an amount of viable cell-derived ATP as an indicator. Table 5 shows IC_{50} of valemetostat.

7) Complex consisting of EZH1 or EZH2, embryonic ectoderm development (EED), suppressor of zeste 12 (SUZ12), retinoblastoma binding protein 4 (RBBP4), and AE binding protein 2 (AEBP2)

Table 5. Growth inhibitory effect of valemetostat against human hematopoietic malignancy cell lines

Cell line	Origin	*EZH1/2* gene mutation	IC_{50} (nmol/L)
KARPAS-422	DLBCL	EZH2 (Y646N*)	12.6
MM.1S	MM	Wild-type	2.19
MV-4-11	AML		1.43
TL-Om1	ATLL		18.4

n = 1; * EZH2 with tyrosine at position 646 substituted by asparagine

3.1.2.2 *In vivo* (CTD 4.2.1.1-7)

Tumor-growth inhibitory effect of valemetostat was investigated using severe combined immunodeficient (SCID) mice subcutaneously implanted with KARPAS-422 cell line expressing mutant EZH2 (Y646N) (n = 6[8)]/group). On Day 22 counted from day of implantation (Day 0), valemetostat was orally administered at 1.56, 6.25, 25, and 100 mg/kg QD or 0.781, 3.13, 12.5, and 50 mg/kg BID for 21 days, followed by calculation of tumor volume. Table 6 shows changes in tumor volume[9)] and TGI.[10)]

Table 6. Tumor-growth inhibitory effect of valemetostat in SCID mice subcutaneously implanted with KARPAS-422 cell line
(top, QD; bottom, BID)

Dose (mg/kg)	Day 42			Day 55		
	n	Change in tumor volume	TGI (%)	n	Change in tumor volume	TGI (%)
1.56	6	721 ± 41	11	3	1,282 ± 40	4
6.25	6	959 ± 92	−18	3	1,320 ± 106	1
25	6	418 ± 88*2	49	3	538 ± 240*1	60
100	6	−32 ± 13*3	>100	3	−190 ± 57*3	>100

Dose (mg/kg)	Day 42			Day 55		
	n	Change in tumor volume	TGI (%)	n	Change in tumor volume	TGI (%)
0.781	6	828 ± 99	−2	3	1,544 ± 160	−16
3.13	6	654 ± 91	20	3	1,180 ± 123	12
12.5	6	369 ± 91*1	55	3	447 ± 160*1	67
50	6	−78 ± 24*3	>100	3	−190 ± 38*3	>100

Mean ± standard error; *1 $P < 0.005$ vs. control (untreated) group (Dunnett test); *2 $P < 0.001$ vs. control (untreated) group (Dunnett test); *3 $P < 0.0001$ vs. control (untreated) group (Dunnett test)

3.2 Safety pharmacology

3.2.1 Effects on central nervous system

In a 4-week repeated-dose toxicity study in rats (n = 8/group) [see Section 5.2], valemetostat was orally administered at 60, 200, and 600 mg/kg QD, and effects of valemetostat on clinical signs were investigated according to the functional observational battery procedure. In all the valemetostat groups, decreased rearing frequency was observed at 8 hours post-dose.

The applicant explained that the above finding is unlikely to cause safety issues in clinical use of valemetostat because C_{max} of plasma unbound valemetostat in rats after the administration of valemetostat 60 mg/kg (males, 0.266 μmol/L; females, 0.553 μmol/L) exceeded C_{max} of plasma

8) On Day 43, of 6 mice per group 3 mice were euthanized for analysis.
9) (Mean tumor volume on day of measurement) – (mean tumor volume on Day 21)
10) TGI (%) = {(change in tumor volume in the control group) – (change in tumor volume in the valemetostat group)}/(change in tumor volume in the control group) × 100

unbound valemetostat in humans after the administration of valemetostat at the recommended dose (200 mg QD) (0.174 μmol/L[11)]).

3.2.2 Effects on cardiovascular system

3.2.2.1 Effects on hERG potassium current (CTD 4.2.1.3-1)

The effect of valemetostat 10, 30, and 100 μmol/L on human *ether-a-go-go*-related gene (hERG) potassium current was investigated using human embryonic kidney HEK293 cell line transfected with hERG. Inhibition rates (mean ± standard error, n = 3) of valemetostat 10, 30, and 100 μmol/L against hERG potassium current were 4.6% ± 2.9%, 7.2% ± 1.2%, and 22.7% ± 3.4%, respectively. Valemetostat 100 μmol/L showed statistically significant inhibition compared with the control (0.1% dimethyl sulfoxide [DMSO]) ($P \leq 0.001$, Dunnett test).

3.2.2.2 Effects on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3-2)

In 4-week (n = 10/group) and 13-week (n = 8-12/group) repeated-dose toxicity studies in dogs [see Section 5.2], valemetostat was orally administered at 15, 30, and 60 mg/kg QD and at 7.5, 15, and 30 mg/kg QD, respectively, and the effect of valemetostat on electrocardiogram[12)] was investigated. QTc interval prolongation was observed in the valemetostat 30 and 60 mg/kg groups.

Valemetostat 15 and 60 mg/kg was orally administered QD to dogs (n = 4/group) for 7 days, and effects on heart rate, blood pressure, and electrocardiogram (PR, QT, QTc, and QRS interval) were investigated. Compared with the control (80% polyethylene glycol 200) group, the valemetostat 60 mg/kg group showed QT interval prolongation at 4, 6, and 8 hours post-dose and QTc interval prolongation at 3, 4, and 8 hours post-dose on Day 7.

The applicant explained that the above finding is unlikely to cause safety issues in clinical use of valemetostat because C_{max} of plasma unbound valemetostat in dogs after the administration of valemetostat 15 mg/kg (males, 1.774 μmol/L; females, 1.863 μmol/L) were approximately 10 times the C_{max} of plasma unbound valemetostat in humans after the administration of valemetostat at the recommended dose (200 mg QD) (0.174 μmol/L[11)]).

3.2.3 Effect on the respiratory system

In the 4-week repeated-dose toxicity study in rats (n = 8/group) [see Section 5.2], valemetostat was orally administered at 60, 200, and 600 mg/kg QD, and effects of valemetostat on respiratory rate, tidal volume, and minute ventilation were investigated. No effects of valemetostat were observed.

3.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that applicant's explanation about non-clinical pharmacology findings of valemetostat is acceptable except for the following.

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11) C_{max} of unbound valemetostat on Day 15 in patients with relapsed or refractory ATLL orally receiving valemetostat 200 mg QD in Study J201.

12) The parameters of which waveform was changed in the electrocardiogram were analyzed.

3.R.1 Mechanism of action and efficacy of valemetostat

The applicant's explanation about the mechanism of action of valemetostat and efficacy in patients with ATLL:

EZH1/2 are components of PRC2 that modulates gene expression through histone modification. By catalyzing the attachment of methyl groups to the lysine residues of proteins such as histone (methylation), EZH1/2 are thought to mediate chromatin condensation, repress gene transcription, etc., thereby being involved in T-cell differentiation and proliferation, etc (*Mol Cell.* 2008;32:503-18).

Infection of human T-cell leukemia virus type 1 (HTLV-1) in normal T-cells perturbs epigenetic gene expression regulation (trimethylation of H3K27, etc.), leading to the activation of T-cell receptor (TCR) and nuclear factor κ B (NF-κB) signaling pathways. This is suggested to be linked to differentiation into ATLL cells and tumor growth (*Cell Rep.* 2019;29:2321-37, etc.). Also, in ATLL, EZH2 that is involved in H3K27 trimethylation is actively expressed (*Blood.* 2016;127:1790-802). The inhibition of the methylation activity of EZH2 thus may lead to the inhibition of tumor-growth. Meanwhile, reports on ATLL showed that when the methylation activity of EZH2 alone is inhibited, the methylation activity may be compensated by EZH1 (*Mol Cell.* 2008;32:491-502 and *Cell Rep.* 2019;29:2321-37). These findings indicate the possibility that both EZH1 and EZH 2 contribute to the proliferation of tumor cells such as in ATLL.

Valemetostat is thought to bind to both EZH1 and EZH2, inhibit their methylation activities [see Section 3.1.1], and alter the expression of genes involved in TCR-mediated apoptosis induction such as src-like adaptor protein (*SLA*) and phosphoprotein associated with glycosphingolipid-enriched microdomains 1 (*PAG1*), thereby inducing apoptosis (*J Cell Biol.* 2005;170:285-94, *Blood.* 2007;110:596-605) leading to tumor-growth inhibition.

In addition, valemetostat has been shown to inhibit growth of the ATLL-derived cell line. In view of these findings, valemetostat is expected to have efficacy in patients with ATLL.

PMDA's review:

PMDA largely accepted the applicant's explanation. However, the degree of contribution of EZH1 or EZH2 to ATLL proliferation and factors affected by the inhibitory effect of valemetostat against trimethylation in ATLL are nearly unexplained, and a direct association between the valemetostat's inhibitory effects on trimethylation activity and tumor-growth inhibition remains unclear. Information about factors affecting the efficacy of valemetostat in patients with ATLL may be critical in predicting the efficacy of valemetostat in clinical use and for identifying eligible patients. The applicant therefore needs to continue collecting information and appropriately update healthcare professionals with new findings whenever available.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In this section, doses and concentrations of valemetostat are expressed as amounts of the free base.

The pharmacokinetics (PK) of valemetostat in animals was investigated in rats, etc. Plasma protein binding, drug-metabolizing enzyme, and transporters of valemetostat were investigated using human or animal biological specimens.

4.1 Absorption

4.1.1 Single-dose study

A single dose of valemetostat 15, 30 and 60 mg/kg was orally administered to male and female dogs, and plasma concentrations of valemetostat were determined (Table 7). No definite differences were observed in the PK of valemetostat between males and females. Over the dose range investigated, the exposure to valemetostat increased nearly in a dose-proportional manner.

Table 7. PK parameters of valemetostat (male and female dogs, single oral administration)

Dose (mg/kg)	Sex	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_t (ng·h/mL)
15	Male	5	2,460 ± 970	1.00 (0.50, 1.00)	10,200 ± 4,220
	Female	5	2,030 ± 476	1.00 (1.00, 2.00)	7,850 ± 1,100
30	Male	5	5,800 ± 545	0.50 (0.50, 1.00)	30,400 ± 7,170
	Female	5	5,360 ± 1,680	1.00 (0.50, 4.00)	28,600 ± 7,600
60	Male	5	8,360 ± 1,660	0.50 (0.50, 1.00)	39,800 ± 21,200
	Female	5	9,240 ± 2,230	1.00 (1.00, 1.00)	41,700 ± 7,020

Mean ± standard deviation (SD); * Median (minimum, maximum)

4.1.2 Repeated-dose study

Valemetostat 20, 60, and 200 mg/kg was orally administered QD to male and female rats for 13 weeks, and plasma concentrations of valemetostat were determined (Table 8). No definite differences were observed in the PK of valemetostat between males and females. C_{max} and AUC_{last} of valemetostat increased in a more than dose-proportional manner over the dose range investigated. The applicant explained that the result might be attributable to saturated excretion into the gastrointestinal lumen owing to the increased dose.

Table 8. PK parameters of valemetostat (male and female rats, repeated oral administration for 13 weeks)

Day of measurement (Day)	Dose (mg/kg)	n	C_{max} (ng/mL)		t_{max} (h)*		AUC_{last} (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
1	20	3	79.4 ± 9.90	141 ± 41.4	4.00 (4.00, 8.00)	2.00 (2.00, 4.00)	518 ± 135	685 ± 210
	60	3	607 ± 184	1,020 ± 247	4.00 (4.00, 4.00)	4.00 (2.00, 4.00)	4,970 ± 897	6,000 ± 1,830
	200	3	2,440 ± 795	3,120 ± 260	4.00 (4.00, 8.00)	8.00 (4.00, 12.00)	20,000 ± 3,020	29,000 ± 5,180
28	20	3	109 ± 22.8	180 ± 79.6	4.00 (4.00, 8.00)	2.00 (2.00, 4.00)	820 ± 130	977 ± 504
	60	3	1,050 ± 218	850 ± 188	4.00 (2.00, 4.00)	2.00 (2.00, 4.00)	6,060 ± 1,720	6,690 ± 1,350
	200	3	4,320 ± 613	2,670 ± 708	4.00 (4.00, 8.00)	8.00 (2.00, 8.00)	32,300 ± 9,360	26,700 ± 9,180
63	20	3	341 ± 195	296 ± 98.5	4.00 (2.00, 4.00)	4.00 (2.00, 4.00)	2,470 ± 1,140	1,880 ± 626
	60	3	1,340 ± 348	1,390 ± 456	2.00 (2.00, 4.00)	4.00 (2.00, 8.00)	10,600 ± 3,660	10,400 ± 1,860
	200	3	4,580 ± 1,550	4,440 ± 418	8.00 (4.00, 8.00)	4.00 (4.00, 8.00)	39,700 ± 11,500	39,600 ± 1,040
90	20	2	208, 590	209, 362	3.00 (2.00, 4.00)	2.00 (2.00, 2.00)	1,110, 5,650	1,910, 2,100
	60	3	1,060 ± 281	1,770 ± 624	4.00 (4.00, 4.00)	2.00 (2.00, 4.00)	8,710 ± 3,520	10,300 ± 732
	200	3	3,350, 5,010	3,360 ± 883	6.00 (4.00, 8.00)	4.00 (4.00, 8.00)	43,500, 44,200	34,700 ± 14,500

Mean ± SD (individual values for n = 2); * Median (minimum, maximum)

4.1.3 *In vitro* membrane permeability

Membrane permeability of valemetostat was investigated using human Colon cancer-derived Caco-2 cell line. The apparent permeability (P_{app}) of valemetostat 10 μmol/L in the presence of a P-glycoprotein (P-gp) inhibitor (verapamil, 100 μmol/L) was 4.87×10^{-6} cm/s. The applicant explained that the membrane permeability of valemetostat is moderate in view of Fa value of valemetostat predicted based on the above result, which fell within a range of the Fa values of moderately membrane-permeable drugs (*J Pharm Sci.* 2016;105:915-24, etc.).

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled valemetostat tosilate (^{14}C-valemetostat) 3 mg/kg was orally administered to male pigmented rats and male albino rats, and tissue distribution of the radioactivity was investigated by quantitative whole-body autoradiography. The radioactivity was shown to be extensively distributed in albino rats. In most of the tissues including blood, the radioactivity concentration peaked by 7 hours post-dose. In albino rats, the maximum tissue radioactivity concentrations in the large intestine, mandibular gland, pituitary gland, pancreas, brown cells, thyroid, and adrenal gland (11,300, 2,440, 1,810, 1,630, 1,440, 1,290, and 1,260 ng Eq./g, respectively) were especially higher than that in blood (35.3 ng Eq./g). Tissue radioactivity concentrations at 168 hours post-dose were below the lower limit of quantification (19.0 ng Eq./g) in most of the tissues. Tissue distribution of the radioactivity in pigmented rats was similar to that in albino rats except for eyeballs and uvea. In pigmented rats, radioactivity concentrations were below the lower limit of quantification (19.0 ng Eq./g) in most of the tissues at up to 168 hours post-dose, while radioactivity was still detected in the eyeballs and uvea at 168 hours post-dose. The above results suggested that valemetostat or its metabolites might bind to

melanin. The applicant, however, explained that valemetostat in clinical use would be unlikely to cause safety issues attributable to the distribution of valemetostat or its metabolites in the melanin-containing tissues, because of no particular safety concerns on the eyes and skin raised in the clinical studies.

4.2.2 Plasma protein binding

Valemetostat (0.6-10 μg/mL) was incubated with mouse, rat, dog, and human plasma specimens at 37°C for 10 minutes followed by ultracentrifugation, and plasma protein binding of valemetostat was investigated. The plasma protein binding of valemetostat was 72.8% to 82.6% in mice, 58.1% to 59.7%, in rats, 58.7% to 74.4% in dogs, and 78.0% to 96.6% in humans.

Valemetostat (0.6-10 μg/mL) was incubated with human serum albumin (4%) and human α1-acid glycoprotein (0.01%) at 37°C for 10 minutes followed by ultrafiltration, and the binding of valemetostat to human serum albumin and human α1-acid glycoprotein was investigated. The binding of valemetostat was 35.0% to 38.7% for human serum albumin and 56.0% to 92.3% for human α1-acid glycoprotein. Based on the above results, the applicant explained that valemetostat mainly binds to α1-acid glycoprotein in human plasma.

4.2.3 Distribution in blood cells

Mouse, rat, dog, and human blood specimens were incubated with ^{14}C-valemetostat (0.3-5 μg/mL) at 37°C for 10 minutes, and distribution of valemetostat in blood cells was investigated. The blood/plasma ratios of valemetostat concentration were 0.88 to 0.95 in mice, 1.22 to 1.23 in rats, 0.78 to 0.86 in dogs, and 0.58 to 0.74 in humans. Based on the above results, the applicant explained that valemetostat is mainly distributed in plasma in humans.

4.2.4 Placental and fatal transfer

Placental and fatal transfer of valemetostat were not investigated. The applicant, however, explained that valemetostat may possibly cross the placenta and be distributed in fetuses in view of teratogenicity found in an embryo-fetal development study in rats [see Section 5.5].

4.3 Metabolism

4.3.1 *In vitro*

Rat, dog, and human hepatocytes were incubated with ^{14}C-valemetostat (10 μmol/L) at 37°C for 4 hours, and metabolites of valemetostat were investigated. No human-specific metabolites were detected, and HM1 and HM4 (both oxidized forms) were detected as main metabolites in human hepatocytes (accounting for 1.8% and 1.6% of the radioactivity, respectively).

Recombinant human cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2B6, CYP 2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5) were incubated with ^{14}C-valemetostat (10 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 30 minutes to identify CYP isoforms involved in the metabolism of valemetostat. The residual rate of valemetostat was 33.7% and 69.6%, respectively, in the presence of CYP3A4 and CYP3A5, and ≥83.8% in the presence of other CYP isoforms investigated. Based on these results, the applicant explained that CYP3A have a major role in the metabolism of valemetostat in humans.

Pharmacokinetic interactions of valemetostat with CYP3A inhibitor and inducer are discussed in Sections "6.2.3.1 Drug-drug interaction study with itraconazole or fluconazole," "6.2.3.2 Drug-drug interaction study with rifampicin," and "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and inducers as well as P-gp inhibitors."

4.3.2 *In vivo*

A single dose of ^{14}C-valemetostat 3 mg/kg was orally administered to bile-duct non-cannulated or cannulated male dogs, and its metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In plasma collected from bile-duct cannulated male dogs, unchanged valemetostat was mainly detected (accounting for 39.4% of the total radioactivity in plasma).
- In urine collected from bile-duct non-cannulated male dogs until 24 hours post-dose, unchanged valemetostat was mainly detected (accounting for 3.5% of the radioactivity administered).
- In feces collected from bile-duct non-cannulated male dogs until 24 hours post-dose, unchanged valemetostat, CALZ-1809a (oxidized form), and CALZ-1810a (*N*-demethylated form) were mainly detected (accounting for 24.8%, 18.6%, and 9.4% of the radioactivity administered).
- In bile collected from bile-duct cannulated male dogs until 24 hours post-dose, unchanged valemetostat was mainly detected (accounting for 15.9% of the radioactivity administered).

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile

A single dose of ^{14}C-valemetostat 3 mg/kg was orally administered to bile-duct non-cannulated male dogs, and urinary and fecal excretion rates of the radioactivity (percentages of the radioactivity administered) were investigated. The urinary and fecal excretion rates of the radioactivity until 168 hours post-dose were 6.0% and 91.0%, respectively.

A single dose of ^{14}C-valemetostat 3 mg/kg was orally administered to bile-duct cannulated male dogs, and biliary excretion rate of the radioactivity (percentage of the radioactivity administered) was investigated. The biliary excretion rate of the radioactivity until 24 hours post-dose was 45.8%.

Based on the above results, the applicant explained that valemetostat and its metabolites are mainly excreted in feces via bile.

4.4.2 Excretion in milk

A single dose of ^{14}C-valemetostat 3 mg/kg was orally administered to lactating female rats, and excretion of valemetostat in milk was investigated. The milk/plasma AUC_{last} ratio of valemetostat was 2.93. Based on the above results, the applicant explained that valemetostat may possibly be excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant explained that clinical use of valemetostat may cause pharmacokinetic interactions mediated by the inhibitory effect of valemetostat against CYP3A in view of C_{max} of unbound valemetostat in plasma (0.174 μmol/L[11)]) after the administration of valemetostat according to the

proposed dosage regimen and the following results. Pharmacokinetic interactions of valemetostat with CYP3A substrates are discussed in Section "6.R.3 Pharmacokinetic interactions with CYP3A substrates and P-gp substrates."

- Valemetostat (0.1-100 μmol/L) was incubated with human liver microsomes in the presence of each substrate of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[13] and NADPH, and the inhibitory effect of valemetostat against each CYP isoform was investigated. Valemetostat inhibited the metabolism of a CYP3A substrate with IC_{50} of 55.2 μmol/L.[14] On the other hand, valemetostat did not clearly inhibit the metabolism of any substrate of the other CYP isoforms investigated.
- Valemetostat (0.1-100 μmol/L) was incubated with human liver microsomes in the presence of NADPH followed by incubation with each substrate of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A),[13] and time-dependent inhibitory effect of valemetostat against each CYP isoform was investigated. Valemetostat did not clearly inhibit the metabolism of the substrate of any CYP isoforms investigated in a time-dependent manner.

4.5.2 Enzyme induction

Human hepatocytes were incubated in the presence of valemetostat (0.1-30 μmol/L) for 3 days, and messenger ribonucleic acid (mRNA) expressions and enzyme activities of CYP1A2, CYP2B6, and CYP3A4 were investigated. Valemetostat did not clearly induce mRNA expression or enzyme activity of any CYP isoform. The applicant explained that clinical use of valemetostat is unlikely to cause pharmacokinetic interactions through the induction of CYP isoforms in view of C_{max} of unbound valemetostat in plasma (0.174 μmol/L[11]) after the administration of valemetostat according to the proposed dosage regimen and the above results.

4.5.3 Transporters

The following results indicated that valemetostat is a substrate of P-gp, multidrug and toxin extrusion (MATE)1, and MATE2-K. Pharmacokinetic interactions of valemetostat with P-gp inhibitors are discussed in Section "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and inducers as well as P-gp inhibitors."

- Transport of ^{14}C-valemetostat (3 μmol/L) mediated by P-gp or breast cancer resistance protein (BCRP) was investigated using Caco-2 cell line. The ratio of the efflux ratio (the ratio of secretion permeability coefficient in the secretive direction to that in the absorptive direction) of ^{14}C-valemetostat was 0.62 and 29.63, respectively, in the presence of a P-gp inhibitor and a BCRP inhibitor[15] whole it was 35.74 in the absence of any inhibitor.
- Using HEK293 cell line expressing human organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, MATE1, or MATE2-K, transport of ^{14}C-valemetostat (0.3-10 μmol/L) was investigated. The ratios of ^{14}C-valemetostat uptake velocity in the cell lines expressing MATE1 and MATE2-K to that in the cell line not expressing MATE1 or MATE2-K were 1.1 to 3.3 and 1.6 to 2.2, respectively. On the other hand, the ratios of ^{14}C-valemetostat uptake velocity in the cell lines expressing OAT1, OAT3, OCT1,

[13] Substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 used were phenacetin, bupropion, paclitaxel, diclofenac, *S*-mephenytoin, and bufuralol, respectively. In addition, substrates of CYP3A used were midazolam and testosterone.
[14] IC_{50} determined using midazolam as a CYP3A substrate. IC_{50} determined using testosterone as the substrate exceeded 100 μmol/L.
[15] The P-gp and BCRP inhibitors used were verapamil (100 μmol/L) and novobiocin (10 μmol/L), respectively.

OCT2, OATP1B1, and OATP1B3 to the cell line not expressing OAT1, OAT3, OCT1, OCT2, OATP1B1, or OATP1B3 were all approximately 1.0.

The applicant explained that clinical use of valemetostat may cause pharmacokinetic interactions through its inhibitory effect against P-gp and MATE1 in view of C_{max} of unbound valemetostat in plasma (0.174 μmol/L[11)]) and estimated valemetostat concentration in the gastrointestinal tract (1,640 μmol/L) after the administration of valemetostat according to the proposed dosage regimen and the following results. Pharmacokinetic interactions of valemetostat with P-gp substrates are discussed in Section "6.R.3 Pharmacokinetic interactions with CYP3A substrates and P-gp substrates."

- The inhibitory effect of valemetostat (0.3-100 μmol/L) against transport of P-gp and BCRP substrates[16)] was investigated using Caco-2 cell line. Valemetostat inhibited transport of a P-gp substrate with IC_{50} of 18.2 μmol/L. On the other hand, valemetostat did not clearly inhibit transport of a BCRP substrate.
- Using mouse kidney S_2 cell line expressing human OAT1 or OAT3, the inhibitory effect of valemetostat (0.3-100 μmol/L) against transport of each transporter substrate[17)] was investigated. Valemetostat did not clearly inhibit transport of either OAT1 or OAT3 substrate.
- Using HEK293 cell line expressing human OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K, the inhibitory effect of valemetostat (0.3-100 μmol/L) against transport of each transporter substrate[18)] was investigated. Valemetostat inhibited transport of OCT1, OCT2, MATE1, and MATE2-K substrates with IC_{50} of 3.98, 5.04, 0.548, and 6.98 μmol/L, respectively. On the other hand, valemetostat did not clearly inhibit transport of either OATP1B1 or OATP1B3 substrate.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted and review of the following section, PMDA has concluded that the applicant's explanation about non-clinical pharmacokinetics of valemetostat is acceptable.

4.R.1 Pharmacokinetic interactions

The applicant's explanation about pharmacokinetic interactions of valemetostat:

Results from *in vitro* studies suggested that pharmacokinetic interactions of valemetostat mediated by MATE1 and MATE2-K might occur [see Section 4.5.3]. Albeit limitations in the evaluation because of the small number of patients who received valemetostat concomitantly with a substrate or inhibitor of the concerned transporter, the following finding indicates that the clinical use of valemetostat is unlikely to cause problems associated with the mentioned pharmacokinetic interactions.

- In a global phase I study (Study J101) and Japanese phase II study (Study J201), the use of valemetostat concomitantly with an MATE1 or MATE2-K inhibitor[19)] or MATE1 substrate[20)] did not raise particular safety concerns.

16) The P-gp and BCRP substrates used were ^{3}H-digoxin (1 μmol/L) and estrone 3-sulfate (0.1 μmol/L), respectively.
17) The OAT1 and OAT3 substrates used were ^{3}H-*p*-aminohippuric acid (1 μmol/L) and ^{3}H-estrone 3-sulfate (50 nmol/L), respectively.
18) The substrates of OCT1, OCT2, MATE1, and MATE2-K as well as OATP1B1 and OATP1B3 used were ^{14}C-metformin (10 μmol/L) and ^{3}H-estradiol-17β-glucuronide (50 nmol/L), respectively.
19) Used concomitantly in 56 and 18 patients in Studies J101 and J201, respectively.
20) Used concomitantly in 5 patients in Study J101 but none in Study J201.

PMDA's review:
PMDA largely accepted the applicant's explanation. Information about pharmacokinetic interactions of valemetostat mediated by MATE1 and MATE2-K is considered to be critical in ensuring proper use of valemetostat, and the applicant is required to provide the concerned information to healthcare professionals using the package insert, continue collecting the information, and appropriately inform healthcare professionals of useful information when it becomes available.

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, doses and concentrations of valemetostat are expressed as amounts of the free base.

5.1 Single-dose toxicity

Single oral dose toxicity studies in rats and dogs were conducted (Table 9). In rats, no acute toxicity was observed at up to the maximum dose (200 mg/kg). In dogs, vomiting, body surface redness or swelling, and high blood histamine concentrations were observed.

In a 14-day repeated-dose toxicity study in dogs (CTD 4.2.3.2-4), vomiting, sedation, tremor, lateral position, staggering gait, redness and feeling hot of limbs, periocular swelling as well as dyspnoea and death occurred in 1 male 4 hours after the first dose of 100 mg/kg.

The applicant explained that the approximate lethal dose of oral valemetostat was >200 mg/kg in rats and 100 mg/kg in dogs.

Table 9. Single dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	0,[a)] 20, 60, 200	None	>200	4.2.3.1-1
Male and female dogs (beagle)	Oral	0,[a)] 15, 30, 60	≥15: Vomiting (male) ≥30: Redness or swelling of auricles, snout, whole body, eyes, and limbs, high blood histamine concentration (male and female), vomiting (female)	>60	4.2.3.1-2

a) 80% polyethylene glycol (PEG) 200 solution

5.2 Repeated-dose toxicity study

In rats and dogs, 4- and 13-week repeated-dose toxicity studies were conducted (Table 10). Toxicity findings in both rats and dogs were low erythroid parameters and related changes, myelopoietic cell decreased, low leukocytic and lymphocytic parameters, atrophy of lymphoid organs and tissues as well as mucosal erosion, degeneration, and mononuclear cell infiltration in the gastrointestinal tract. The other findings included lymphoma and pleonosteosis of the bone in rats; and QT interval prolongation, high blood histamine concentrations, redness or swelling of the whole body and auricles associated with histamine release, erosion, ulcer, and inflammatory changes of the skin as well as effects on the male and female reproductive organs in dogs [see Section 5.5]. In the repeated-dose toxicity studies in rats and dogs, toxicity was evaluated from a viewpoint of tolerability, and no-observed-adverse-effect level (NOAEL) has not been determined. The applicant explained that high incidences of inflammatory

changes in the skin in the valemetostat groups suggested potential skin contact with valemetostat although the exposure route remains unknown.

Table 10. Repeated-dose toxicity

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	4 weeks (QD) + 4-week recovery	0,[a)] 60, 200, 600	<u>Dead animals</u> 600: 3 of 15 females <u>Survived animals</u> ≥60: Low white blood cell count, neutrophil count, basophil count, lymphocyte count, and large unstained cell count; small size and atrophy of the thymus (male and female); decreased rearing frequency[b)] (male); high reticulocyte count (female) 200: Alopecia; low red blood cell count, hemoglobin, and hematocrit (male and female); scab; reduced body weight gain (male) 600 (early sacrificed[c)]): Dyspnoea, hunchback position, severe sedation, piloerection, salivation, low body weight and food consumption, high hemoglobin and hematocrit values, low platelet count, reticulocyte count, and monocyte count, high neutrophil count and eosinophil count, prolonged prothrombin time and APTT, high blood glucose and urea nitrogen values, low blood total protein potassium values, high adrenal weight, decreased myeloid cell count, focal or multiple dark lesions and depressed lesions in the stomach, mucosal erosion and inflammation in the glandular stomach, dilation of and liquid contents in the cecum, inflammation and mucosal epithelium degeneration in the ileum and cecum, lymphocytic hyperplasia and lymphocytic atrophy in the spleen, cortical atrophy of the mesenteric lymph node and submandibular lymph node (male and female), decrease in locomotor activity,[b)] high blood cholesterol and creatinine values, low blood fibrinogen and inorganic phosphorus values, multiple cortical brown lesions and renal tubular degeneration in the kidney, dilation of and liquid contents in the ileum and colon, lymphocyte depletion in the Peyer's patch (male), high red blood cell count, high blood creatine kinase and glutamate dehydrogenase values, low blood albumin value (female) After end of the recovery period None	-	4.2.3.2-2
Male and female rats (Sprague Dawley)	Oral	13 weeks (QD) + 4-week recovery	0,[a)] 20, 60, 200	<u>Dead animals</u> 20: 1 of 15 males, 3 of 15 females Dyspnoea, crouching position, lymphoma cell infiltration in the bone marrow, heart, jejunum, ileum, kidney, liver, lung, lymph node, spleen, and thymus (male and female), lymphoma cell infiltration in the brain meninges, ovary, femur, pituitary gland, and salivary gland (female) 200: 8 of 15 males, 2 of 15 females Dyspnoea, crouching position (male and female), pleonosteosis of the skull (male) <u>Survived animals</u>	-	4.2.3.2-3

				20: Thymus lymphoma (male and female), lymphoma cell infiltration in the bone marrow, spleen, lymph node, heart, liver, lung, jejunum, and ileum (male) ≥20: Nasal red discharge, lymphoblastic hyperplasia and lymphocytic atrophy in the thymus (male and female), ocular red discharge, low fibrinogen value (male), pleonosteosis of the sternum (female) ≥60: Redness of the auricles and snout, low total protein value in blood, low thymus weight, myelopoietic cell hyperplasia, pleonosteosis of the femur and tibia (male and female), swelling of snout, high adrenal weight, hepatocyte hypertrophy in the liver, pleonosteosis of the sternum, splenic red pulp atrophy (male), ocular red discharge, high spleen weight, lymphocytic atrophy in the mesenteric lymph node (female) 200: Alopecia, piloerection, oral red discharge, red face and head, low red blood cell count, hemoglobin, and hematocrit values, low white blood cell count and lymphocyte count, lymphocytic atrophy in the submandibular lymph node, glandular and epithelial hyperplasia in the cecum and colon (male and female), low body weight and food consumption, low testis weight, seminiferous epithelium degeneration and atrophy in the testis, decreased epididymis luminal sperms, atrophy of the prostate gland, vesicular gland, and mammary gland, adrenal vacuolation, lymphocytic atrophy in the mesenteric lymph node (male), swelling of snout, choroidal diffuse anemia, narrow opthalmovascular lumen, hepatocyte hypertrophy in the liver, atrophy of the ovary, uterus, and vagina, splenic red pulp atrophy (female)		
				After end of the recovery period[d)] ≥60: Pleonosteosis of the femur, tibia, and sternum (male and female) 200: Seminiferous epithelium depletion in the testis, decreased epididymis luminal sperms (male)		
Male and female dogs (beagle)	Oral	4 weeks (QD) + 4-week recovery	0,[a)] 15, 30, 60	<u>Dead animals</u> 60: 5 of 5 males, 2 of 5 females Low reticulocyte count, high blood fibrinogen, total bilirubin, and cholesterol values, low blood potassium and chloride values, faded and discolored lesions in the colon, decreased mucosal epithelium, mononuclear cell infiltration, and mucosal epithelium degeneration in the small intestine and large intestine, atrophy of the Peyer's patch, decreased myelopoietic cell count, lymphocytic atrophy in the spleen and mesenteric lymph node, tubular degeneration in the kidney (male and female), high blood urea nitrogen, creatinine, and inorganic phosphorus values, high adrenal gland and kidney weights, faded and discolored lesions in the rectum, small thymus (male), faded and discolored lesions in the stomach and jejunum, small submandibular lymph node (female) <u>Survived animals</u> ≥15: Vomiting, salivation, high white blood cell count and neutrophil count, high blood triglyceride and glucose values (male), redness	-	4.2.3.2-5

				of the limbs, low white blood cell count and lymphocyte count (female) 30: Mononuclear cell inflammation in the stomach (female) ≥30: Redness and swelling of the whole body and auricles, low red blood cell count, hemoglobin value, hematocrit value, and platelet count, high blood histamine value, thymus atrophy, lymphocytic atrophy in the spleen (male and female), listlessness (male), vomiting, salivation, QTc interval prolongation, high blood triglyceride and glucose values, lymphocytic atrophy in the mesenteric lymph node (female) 60: Green feces (male and female), blackish feces (male), listlessness, low body weight and food consumption, low blood potassium value (female)		
				After end of the recovery period None		
Male and female dogs (beagle)	Oral	13 weeks (QD) + 4-week recovery	0,[a)] 7.5, 15, 30	<u>Dead animals</u> 30: 4 of 6 males Edema of the limbs, eyes, and auricles, low white blood cell count, high urine bilirubin and creatinine values, urinary occult blood, skin epidermis erosion, epidermal ulcer, dermal vasodilatation, and subcutaneous tissue vasodilatation of the scrotum, seminiferous epithelium degeneration in the testis <u>Survived animals</u> ≥7.5: Low blood total protein and albumin values, lymphocytic atrophy in the thymus, submandibular gland, mesenteric lymph node, and intestinal lymphoid tissue, myelopoietic cell hyperplasia, enhanced extramedullary hematopoiesis in the spleen (male and female), skin redness, low testis weight, high adrenal gland weight, multiple-lesion lymphoblastic hyperplasia in the thymus, seminiferous epithelium atrophy, interstitial cell hypertrophy, and hyperplasia in or of the testis, decreased epididymis luminal sperms (male), low thymus weight (female) ≥15: Low red blood cell count, hemoglobin value, and hematocrit value, high erythroid count and low granulocyte count in the bone marrow, low M/E ratio in the bone marrow (male and female), salivation, open wound of the paw, skin laceration, perivascular mixed-cell inflammation, epidermis degeneration, and epidermis hyperplasia in or of the scrotum, large erythroblasts, normoblasts (male), skin redness, conjunctivitis, multi-lesion lymphoblastic hyperplasia in the thymus, yellow pigmentation in the hepatic Kupffer cells, yellow discharge, redness, thickening, and mixed-cell inflammation in the bilateral conjunctivae (female) 30[e)]: Redness of the limbs, eyes, and auricles, high blood histamine concentration (male and female), conjunctivitis (male), salivation, vomiting, diarrhea, eyelid edema, vulval swelling, open wound of the paw, low white blood cell count, high fibrinogen value, large erythroblasts, normoblasts, perivascular mixed-cell inflammation in the periocular skin, degeneration and inflammation of the	-	4.2.3.2-6

				epidermis, unilateral interstitial inflammation in the cornea (female)		
				After end of the recovery period[d)] ≥15: Seminiferous epithelium atrophy in the testis, decreased epididymis luminal sperms (male) 30: Inflammation in the conjunctiva (male and female)		

a) 80% PEG200 solution
b) Functional observation battery test was performed only on males.
c) All the animals were sacrificed on Day 10 or 11 owing to worsening of clinical signs.
d) Irreversible or potentially irreversible findings are listed.
e) In the 30 mg/kg group, 2 males were withdrawn from the study treatment on Day 51 and sacrificed on Day 84.
-, No NOAEL was evaluated.

5.3 Genotoxicity

Bacterial reverse mutation assay (Ames test), *in vitro* micronucleus assay in Chinese hamster lung (CHL) cell line, and *in vivo* bone marrow and liver micronucleus assay in rats were conducted (Table 11). The applicant explanation that valemetostat induced micronucleus formation with metabolic activation in the *in vitro* assay but did not induce it in the *in vivo* assay in rats, and thus valemetostat is unlikely to be genotoxic.

Table 11. Genotoxicity study

Type of study		Test system	Metabolic activation (treatment)	Concentrations or dose	Result	Attached document CTD
In vitro	Ames test	*Salmonella typhimurium:* TA98, TA100, TA1535, TA1537 *Escherichia coli:* WP2*uvrA*	S9-	0,[a)] 39.1, 78.1, 156, 313, 625, 1,250, 2,500, 5,000 µg/plate	Negative	4.2.3.3.1-1
			S9+	0,[a)] 78.1, 156, 313, 625, 1,250, 2,500, 5,000 µg/plate		
	Micronucleus	CHL cell line	S9- (6 hours)	0,[a)] 0.3, 0.35, 0.4 mmol/L	Negative	4.2.3.3.1-2
			S9- (26 hours)	0,[a)] 0.125, 0.15, 0.175 mmol/L	Negative	
			S9+ (6 hours)	0,[a)] 0.025, 0.05, 0.1, 0.125, 0.15, 0.175 mmol/L	Positive	
In vivo	Micronucleus	Male rat (Sprague Dawley) Single oral dose, bone marrow		0,[b)] 100, 300, 1,000, 2,000 mg/kg	Negative	4.2.3.3.2-1
		Male rat (Sprague Dawley) Oral (administered about 24 hours before and after partial hepatectomy), liver		0,[b)] 100, 300, 1,000, 2,000 mg/kg	Negative	4.2.3.3.2-2

a) DMSO; b) 80% PEG200 solution

5.4 Carcinogenicity

Because valemetostat is an antineoplastic agent intended to treat patients with advanced cancer, no carcinogenicity studies were conducted. In the 13-week repeated-dose toxicity study in juvenile rats[21)] (CTD 4.2.3.2-3), thymus lymphoma was observed in the valemetostat group, but in the same toxicity study in aged rats[22)] (CTD 4.2.3.7.3-4), no such finding was observed (Table 12).

[21)] Treatment was started in rats at 8 weeks of age.
[22)] Treatment was started in rats at 55 weeks of age.

Table 12. Thirteen-week repeated-dose toxicity studies in juvenile and aged rats (thymus lymphoma)

Test system	Route of administration	Dosing period	Main lesions	Sex	Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					Vehicle	Valemetostat					
					0[b)]	10	20	60	200		
Male and female rat (SD) 8 weeks of age[a)]	Oral	13 weeks (QD)	Tumor lesion							-	4.2.3.2-3
			Thymus/ lymphoma	M	0/10[c)]	NE	3/9	0/9	0/3		
				F	0/10	NE	2/9	0/10	0/8		
Male rat (SD) 55 weeks of age[a)]	Oral	13 weeks (QD)	Tumor lesion							20	4.2.3.7.3-4
			Thymus/ lymphoma	M	0/20	0/30	0/30	NE	NE		
			Other findings								
			≥10: High eosinophil count, low large unstained cell count and neutrophil count 20: Low white blood cell count, lymphocyte count, and $CD4^+$ T-cell count, high thymic $CD8^+$ T-cell count								

a) Age (weeks) at the first dose
b) 80% PEG200 solution
c) Number of animals with the finding/number of animals evaluated
NE, Not evaluated; -, Not calculated

5.5 Reproductive and developmental toxicity

In the 13-week repeated-dose toxicity studies in rats and dogs, the effects on male and female reproductive organs were evaluated. The findings were seminiferous epithelium degeneration and decreased epididymis luminal sperms in the testis in rats and dogs, atrophy of the prostate gland and vesicular gland in male rats, and atrophy of the ovary, uterus, and vagina in female rats [see Section 5.2].

An embryo-fetal development study in rats was conducted (Table 13). At the lowest dose of 20 mg/kg/day, a high percentage of postimplantation loss, all embryonic/fetal deaths, and skeletal malformation were observed. NOAEL has not been determined.

The above study results revealed toxicity and teratogenicity of valemetostat in embryos and fetuses and do not clearly show a sufficient difference between the clinical exposure and the exposure at which the toxicity and teratogenicity were observed. In view of these findings, the applicant explained that the following points will be included in package insert, etc. to raise cautions among healthcare professionals:

- Physicians should advise women of childbearing potential and men with a female partner of childbearing potential to use appropriate contraception during treatment with valemetostat and for a certain period after the end of the treatment.
- Valemetostat is an antineoplastic agent intended to treat patients with serious advanced cancer with limited therapeutic options, valemetostat should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

Table 13. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development	Female rats (Sprague Dawley)	Oral	Gestation Days 7-17 (QD)	0,[a] 20, 60, 200	Maternal animals: ≥20: Low body weight gain ≥60: Low body weight and food consumption Embryos and fetuses[b]: 20: High number/ percentage of fetuses with skeletal malformation or variation, rib defect,[c] thoracic vertebra defect,[c] lumbar vertebra defect,[c] cervical rib,[d] short and/or small ribs,[d] thoracic vertebra split[d] ≥20: High postimplantation loss ≥60: All embryonic/fetal deaths	Maternal animals (general toxicity): - Embryos-fetuses: -	4.2.3.5.2-1 (reference)

a) 80% PEG200 solution
b) The embryo-fetal examination was not conducted in the 60 and 200 mg/kg/day groups.
c) Malformation finding
d) Variation finding
-, Not calculated

5.6 Other toxicity studies

5.6.1 Photosafety

A phototoxicity testing was conducted using mouse fibroblasts (Table 14). The applicant explained that valemetostat had no phototoxicity.

Table 14. Photosafety study

Type of study	Test system	Test method	Result	Attached document CTD
In vitro	Mouse fibroblasts (Balb/c 3T3)	0,[a] 0.781, 1.56, 3.13, 6.25, 12.5, 25.0, 50.0, 100 μg/mL UVA irradiation (50 minutes, 5 J/cm^2)	PIF, -[b]; MPE, -0.008 No phototoxicity	4.2.3.7.7-1

a) DMSO
b) Not calculated because of no cytotoxicity found

5.6.2 Studies for mechanism of development of toxicity

In the 13-week repeated-dose toxicity study of valemetostat in rats, thymus lymphoma was observed [see Section 5.2], and studies for the mechanism of development of thymus lymphoma were conducted (Table 15). The applicant explained that lymphocyte subset analysis and gene expression profiling indicated that thymus lymphoma observed in the above study was derived from T-cells and might have been caused by variations of oncogenes, tumor suppressor genes, and T-cell differentiation-related genes.

Table 15. Studies for mechanism of development of toxicity

Test system	Test method	Main findings	Attached document CTD
Male and female rats (Sprague Dawley)	Immunohistochemical staining of thymus, kidney, spleen, lymph node, liver, and lung specimens from the 13-week repeated oral dose toxicity study in rats (CTD 4.2.3.2-3)	Thymus-lymphoma-derived lymphocytic cells observed in the thymus, kidney, spleen, lymph node, liver, and lung were CD3ε^+, CD8α^+, and CD79α^-	4.2.3.7.3-1 (reference)
Male rat (Sprague Dawley)	Rats which orally received valemetostat 0[a)] and 20 mg/kg/day QD for 1, 2, and 3 months were subjected to histopathological examination of thymus, lymphocyte subset analysis on peripheral blood and thymus, clonality analysis as well as gene expression analysis.	Thymus lymphoma developed after at least 2 months of treatment. Changes in animals with lymphoma High DN T-cell count, DP T-cell count, CD3$^+$ T-cell count, CD4$^+$ T-cell count, and CD8$^+$ T-cell count, and high B-cell count and NK-cell count in peripheral blood; high DN T-cell count, CD3$^+$ T-cell count, and CD8$^+$ T-cell count in the thymus; multiple *TCRβ* gene rearrangement patterns, increased expression of oncogenes (*Myc, Bcl2*, etc.), decreased expression of tumor suppressor genes (*E2f2, Tp63*, etc.), and varied expression of T-cell differentiation-related genes (*Cd4, Cd83, Cd28, Tfap4*, etc.) in the thymus	4.2.3.7.3-2 (reference)
Male rat (Sprague Dawley)	Rats which orally received valemetostat 0,[a)] 20, and 60 mg/kg/day QD for 2 and 3 months were subjected to histopathological examination, lymphocyte subset analysis on thymus and peripheral blood, gene expression analysis, whole-genome sequencing as well as clonality analysis.	20: Findings in rats which received the treatment for 2 or 3 months and were found to have thymus lymphoma or lymphoma were high DN T-cell count, DP T-cell count, αβ$^+$ T-cell count, CD3$^+$ T-cell count, and CD8$^+$ T-cell count in peripheral blood and thymus; increased expression of MYC-target genes, DN T-cell-related genes, and Treg-related genes in thymus DP T-cells; decreased expression of interferon-related genes in thymus DP and CD8$^+$ T-cells; no induction of mutations, copy number anomaly, or structural aberration in genome; and multiple *TCRβ* gene rearrangement patterns in animals with lymphoma	4.2.3.7.3-3 (reference)

a) 80% PEG200 solution

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and a review of the following section, PMDA has concluded that the applicant's explanation about toxicity of valemetostat is acceptable.

5.R.1 Thymus lymphoma

The applicant's explanation about the mechanism of development of lymphoma, which was observed in the 13-week repeated oral dose toxicity study in juvenile rats [see Section 5.4], and safety of valemetostat in target patients:

Thymus lymphoma observed in the valemetostat group was derived from T-cells [see Section 5.6.2]. T-cell lymphoma was observed in EZH2-conditional knock-out mice at an adult stage (*Genes Dev.* 2012;26:651-6). These findings suggest that the development of thymus lymphoma in juvenile rats may be related to the inhibitory effect of valemetostat against EZH2,

In addition, loss-of-function mutation or reduced expression of EZH2 contributes to the development of childhood T-cell lymphoma (*J Cancer Res Clin Oncol.* 2016;142:1641-50), and thus the use of valemetostat in children can cause T-cell lymphoma. In contrast, thymus lymphoma did not occur in aged rats which were repeatedly treated with valemetostat at the same dose for the same period as in juvenile rats that developed thymus lymphoma after the treatment. Based on this finding , a risk of T-

cell lymphoma associated with valemetostat is considered to be low in adult patients with ATLL in whom the thymus tends to be involuted with age.

PMDA's review:
In view that (a) no thymus lymphoma was observed in the 13-week repeated-dose toxicity study of valemetostat in aged rats; and (b) patients with ATLL, the intended population of valemetostat, are presumed to have had thymic involution as in aged rats, the applicant's explanation about the risk of lymphoma associated with valemetostat is understandable to a certain extent. It is difficult at present, however, to draw a definite conclusion about the risk of the T-cell-derived lymphoma associated with valemetostat in patients with ATLL, because thymus lymphoma is thought to be associated with the inhibitory effect of valemetostat against EZH2, and exposure to the dose leading to thymus lymphoma is below the clinical exposure. Therefore, the applicant should raise caution about the occurrence of lymphoma in the toxicity studies of valemetostat appropriately using the package insert, etc. and to continue collecting information in post-marketing settings.

5.R.2 Pleonosteosis of bones

The applicant's explanation about the mechanism of development of pleonosteosis of the femur, tibia, and sternum, which was observed in the 13-week repeated-dose toxicity study in rats [see Section 5.2], and safety of valemetostat in target patients:
Although the inhibitory effect of valemetostat against EZH1 or EZH2 may affect osteogenesis (*Cell Prolif.* 2021;54:e13032, *Nat Commun.* 2016;7:13685), the relationship with pleonosteosis remains unclear. Clinical use of valemetostat is unlikely to raise safety issues in view that (a) patients with ATLL, the intended population of valemetostat, are old enough to have closed epiphyses and be out of a bone-growth stage; and (b) no adverse events related to osteogenesis occurred in subjects treated with valemetostat in clinical studies.

PMDA accepted the applicant's explanation.

5.R.3 Effects on male and female reproductive organs

The applicant's explanation about the mechanism of how the toxicity develops in the male and female reproductive organs as observed in the 13-week repeated-dose toxicity studies in rats and dogs [see Section 5.2], and the safety of valemetostat in target patients:
In male and female reproductive organs of EZH2-conditional knock-out mice, atrophic changes observed as toxicity in the above toxicity studies were not observed (*Reproduction.* 2017;154:615-25, *Biol Reprod.* 2019;101:306-17). The inhibited sperm formation in the testis and atrophic changes in the female reproductive organs are therefore considered to have resulted from decreased hormone secretion but not the inhibitory effect of valemetostat against EZH1 or EZH2. A detailed mechanism of the development, however, remains unclear. In addition, the toxicity findings in the testis were observed with exposure less than the clinical exposure and hardly reversible in dogs, and thus male patients treated with valemetostat may experience testis toxicity and decreased fertility. The applicant therefore plans to raise caution about the effects on the male and female reproductive organs among healthcare professionals appropriately using package insert, etc.

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Oral valemetostat are available in liquid, capsules, and tablets, and the PK of valemetostat was investigated using these formulations (Table 16). Proposed commercial formulation is 50 and 100 mg tablets. Bioequivalence between the 50 mg and 100 mg tablets, proposed commercial formulations, was verified by dissolution test, which was performed in accordance with the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000).

Table 16. Formulations used in clinical studies

Formulation	Study ID
Oral liquid containing ^{14}C-valemetostat	Foreign phase I study (Study U105)
Capsule (25 and 100 mg)	Japanese phase I study (Study J103[*1]), global phase I study (Study J101)
Tablet (25 and 100 mg)	Japanese phase I study (Studies J103, J104,[*2] J107,[*3] and J109[*3]), global phase I study (Study J101), foreign phase I study (Study U106[*2]), Japanese phase II study (Study J201[*4])

[*1] 100 mg capsules were used.
[*2] 25 mg tablets were used.
[*3] 100 mg tablets were used.
[*4] 25 mg tablets were used for dose reduction.

6.1.1 Assay

Amounts of valemetostat in human plasma and urine were determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification was 1.00[23] and 100 ng/mL, respectively.

6.1.2 Japanese clinical studies

6.1.2.1 Japanese phase I study (CTD 5.3.1.1-1, Study DS3201-A-J103 [Study J103] Part 2, [redacted] 20[redacted] to [redacted] 20[redacted])

A 2-treatment, 2-period crossover study was conducted in 32 healthy adults (30 subjects included in the PK analysis)[24] to determine relative BA of tablets to capsules and investigate the effect of food (high-fat meal) on the PK of valemetostat (tablet). The following dosage regimens were used with an 8- to 10-day washout period between the doses:

Group 1: A single dose of valemetostat (capsule or tablet) 200 mg was orally administered to subjects in the fasted state.[25]

Group 2: A single dose of valemetostat (tablet) 200 mg was orally administered to subjects in the fasted state[25] or after a high-fat meal (a total of about 800-1,000 kcal, of which about 500-600 kcal is from fat).

[23] Plasma specimens in the foreign phase I study (Study DS3201-A-U105 [Study U105]) were analyzed by a method with the lower limit of quantification being 20 ng/mL.
[24] The target sample size was 16 subjects for each of Groups 1 and 2 (15 subjects each included in the PK analysis). From the PK analysis, 2 subjects who did not receive the study drug during a part of the treatment period were excluded.
[25] Administered after ≥10-hour fasting, followed by ≥4-hour fasting

In Group 1, the least squares geometric mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{inf} of valemetostat after administration with tablets to those after administration with capsules were 0.956 [0.832, 1.100] and 0.988 [0.874, 1.117], respectively. In Group 2, the least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of valemetostat after administration in the high-fat meal-fed state to those after administration in the fasted state were 0.487 [0.297, 0.800] and 0.703 [0.495, 1.000], respectively. The median t_{max} of valemetostat after administration in the fasted state and in the high-fat meal-fed state was 3.0 and 6.0 hours, respectively.

6.1.2.2 Japanese phase I study (CTD 5.3.1.1-2, Study DS3201-A-J109 [Study J109], October 2020 to January 2021)

A 2-treatment, 2-period crossover study was conducted in 28 healthy adults (28 subjects included in the PK analysis) to investigate the effect of food (low-fat meal) on the PK of valemetostat (tablet). A single dose of valemetostat (tablet) 200 mg was orally administered to subjects in the fasted state[25)] or after a low-fat meal (a total of about 400-500 kcal, of which about 100-125 kcal is from fat) with an 8-day washout period between the doses.

The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of valemetostat after administration in the low-fat meal-fed state relative to those after administration in the fasted state were 0.375 [0.246, 0.571] and 0.466 [0.327, 0.663], respectively. The median t_{max} of valemetostat after administration in the fasted state and in the low-fat meal-fed state was 3.0 and 5.5 hours, respectively.

Regarding the above results and data from Part 2 of the Japanese phase I study (Study J103) [see Section 6.1.2.1], the applicant explained that decreased absorption in the upper gastrointestinal tract might have lowered C_{max} and AUC_{inf} of valemetostat, and slowed gastric emptying rate might have delayed the t_{max}.

6.1.3 Effects of stomach pH on the PK of valemetostat

Solubility of valemetostat is 1.7 to 2.1 mg/mL[26)] within a range investigated and was not clearly impacted by pH. In view of these findings, the applicant explained that gastric pH increased by proton pump inhibitors would be unlikely to have an effect on the PK of valemetostat.

6.2 Clinical pharmacology

The PK of valemetostat in healthy adults and patients with cancer was investigated after the administration of valemetostat alone or in combination with itraconazole, fluconazole, or rifampicin.

6.2.1 Global clinical study

6.2.1.1 Global phase I study (CTD 5.3.3.2-1; Study J101, Up-titration and dose expansion part; ongoing since March 2016 [data cut-off on November 2, 2020])

An open-label, uncontrolled study was conducted in 78 patients with relapsed or refractory NHL, ATLL, or peripheral T-cell lymphoma (PTCL) (77 patients included in the PK analysis) to investigate the PK

[26)] Determined using hydrochloric acid (0.1 mol/L) as well as the 1st and 2nd fluids for dissolution test in the Japanese pharmacopeia

of valemetostat.[27] Valemetostat was orally administered in the fasted state QD at 150, 200, 250, and 300 mg in the dose escalation part and 200 mg in the dose expansion part.

Table 17 shows PK parameters of valemetostat.

Table 17. PK parameters of valemetostat

Dose (mg)	Day of measurement (Day)	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
150	1	7	1,920 (55.0)	2.07 (1.00, 3.95)	13,400 (75.9)	8.15 (25.0)
	15	7	1,460 (46.3)	2.00 (0.58, 6.02)	10,400 (27.7)*2	9.87 (54.9)*3
200	1	61	1,640 (94.3)	3.93 (0.17, 22.90)	12,200 (97.2)*4	8.98 (68.9)*5
	15	57	1,830 (79.1)	3.78 (0.00, 6.05)	15,200 (74.8)*6	9.93 (27.9)*7
250	1	7	1,630 (75.6)	3.92 (1.02, 4.07)	11,900 (63.8)	8.44 (13.0)
	15	7	1,510 (51.2)	3.90 (1.03, 4.03)	13,700 (53.0)	10.2 (16.6)
300	1	2	2,540, 8,290*8	2.03, 3.98*8	11,000, 78,500	3.08, 8.09*8
	15	2	2,060, 6,600*8	3.97, 4.17*8	19,200, 72,900	7.47*9

Geometric mean (coefficient of variation [CV] %) (individual values for n = 1 or 2)
*1 Median (minimum, maximum); *2 n = 6; *3 n = 4; *4 n = 53; *5 n = 39; *6 n = 50; *7 n = 37; *8 n = 2; *9 n = 1

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.1-1, Study DS3201-A-U105 [Study U105], ■ to ■ 20■)

An open-label, uncontrolled study was conducted in 8 healthy adults (8 subjects included in the PK analysis) to investigate the mass balance. A single dose of ^{14}C-valemetostat about 200 mg was orally administered in the fasted state to determine radioactivity concentrations in plasma, urine, and feces.

In plasma until 360 hours post-dose, unchanged valemetostat and CALZ-1809a (oxidized form) were mainly detected (AUC_{inf} of unchanged valemetostat corresponded to 54.6%[28] of that of the total radioactivity).

Until 360 hours post-dose, 15.6% and 79.8% of the radioactivity administered were excreted into urine and feces, respectively. In urine until 360 hours post-dose, unchanged valemetostat was mainly detected (accounting for 10.0% of the radioactivity administered). In feces until 360 hours post-dose, unchanged valemetostat and CALZ-1809a were mainly detected (accounting for 64.9% and 5.6% of the radioactivity administered, respectively).

6.2.3 Drug-drug interaction studies

6.2.3.1 Drug-drug interaction study with itraconazole or fluconazole (CTD 5.3.3.4-1, Study DS3201-A-J104 [Study J104], ■ to ■ 20■)

An open-label study was conducted in 32 healthy adults (29 subjects included in the PK analysis)[29] to investigate the effect of itraconazole (drug that potently inhibits CYP3A and P-gp) or fluconazole (moderate CYP3A inhibitor) on the PK of valemetostat. The dosage regimens applied were as follows:

[27] Study J101 was designed to have a DDI cohort to investigate the effect of valemetostat on midazolam or digoxin in patients with relapsed or refractory NHL, but no patients were enrolled in the DDI cohort as of data cut-off. No results in the DDI cohort are thus included in the clinical study report of Study J101.
[28] AUC_{inf} of CALZ-1809a corresponded to 83.0% of that of valemetostat.
[29] Groups 1 and 2 each included 16 subjects (16 and 13 subjects included in the PK analysis, respectively).

Group 1: A single dose of valemetostat 25 mg was orally administered on Days 1 and 11; and itraconazole 200 mg was orally administered BID on Day 6 and then QD from Days 7 to 20.
Group 2: A single dose of valemetostat 25 mg was orally administered on Days 1 and 12; and fluconazole was orally administered QD at 400 mg on Day 6 and then at 200 mg from Days 7 to 18.

The least-squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of valemetostat after concomitant use of valemetostat with itraconazole and fluconazole to those after the administration of valemetostat alone were 2.92 [2.26, 3.78] and 4.19 [3.45, 5.09], respectively, for itraconazole, and 1.61 [1.12, 2.32] and 1.58 [1.23, 2.04], respectively, for fluconazole.

6.2.3.2 Drug-drug interaction study with rifampicin (CTD 5.3.3.4-2, Study DS3201-A-J107 [Study J107], July to ■ 2020)

An open-label study was conducted in 20 healthy adults (20 subjects included in the PK analysis) to investigate the effect of rifampicin (potent CYP3A inducer) on the PK of valemetostat. A single dose of valemetostat 200 mg was orally administered on Days 1 and 16; and rifampicin 600 mg was orally administered QD from Days 8 to 22.

The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of valemetostat after concomitant use of valemetostat with rifampicin to those after the administration of valemetostat alone were 0.417 [0.319, 0.545] and 0.286 [0.225, 0.364], respectively.

6.2.4 Foreign phase I study for effect of hepatic impairment on the PK of valemetostat (CTD 5.3.3.3-1, Study DS3201-A-U106 [Study U106], January 2020 to February 2021)

An open-label, uncontrolled study was conducted in 8 healthy adults (8 subjects included in the PK analysis) and 16 patients with mild and moderate hepatic impairment[30)] (8 subjects for each severity, 8 subjects each included in the PK analysis) to investigate the effect of hepatic impairment on the PK of valemetostat. A single dose of valemetostat 50 mg was orally administered, and plasma concentrations of valemetostat were determined.

The least-squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of unbound valemetostat in patients with mild and moderate hepatic impairment to those in healthy adults were 0.701 [0.413, 1.19] and 0.811 [0.474, 1.39] and 1.23 [0.795, 1.89] and 1.15 [0.755, 1.76], respectively.

The applicant's explanation about the use of valemetostat in patients with hepatic impairment based on the above results:
Dose adjustment for patients with mild or moderate hepatic impairment is unnecessary because mild or moderate hepatic impairment is deemed to have no clear effect on the PK of valemetostat. In view that valemetostat is mainly eliminated through hepatic metabolism [see Section 6.2.2.1], the clinical study did not include patients with severe hepatic impairment, which will be informed through the package insert.

30) Classified according to the criteria of National Cancer Institute Organ Dysfunction Working Group (NCI- ODWG).

6.2.5 Use of valemetostat in patients with renal impairment

No clinical study was conducted in patients with renal impairment to investigate the effect of renal impairment on the PK of valemetostat.

The applicant's explanation:

Dose adjustment of valemetostat is not necessary in patients with renal impairment, in view of the following points.

- Results of the foreign phase I study (Study U105) suggested that renal excretion contributes only minimally to the elimination of valemetostat [see Section 6.2.2.1].
- In the global phase I study (Study J101), incidences of (a) Grade ≥3 adverse events (b) serious adverse events, (c) adverse events leading to interruption, (d) adverse events leading to dose reduction, and (e) adverse events leading to treatment discontinuation in patients with normal renal function[31)] (n = 26), patients with mild renal impairment (n = 27), and patients with moderate renal impairment (n = 24) were (a) 65.4%, 70.4%, and 75.0%, (b) 38.5%, 29.6%, and 20.8%, (c) 42.3%, 44.4%, and 37.5%, (d) 7.7%, 7.4%, and 16.7%, and (e) 0%, 3.7%, and 4.2%, respectively. The incidences did not show any clear relationship with renal impairment.
- In the Japanese phase II study (Study J201), incidences of (a) Grade ≥3 adverse events (b) serious adverse events, (c) adverse events leading to interruption, (d) adverse events leading to dose reduction, and (e) adverse events leading to treatment discontinuation in patients with normal renal function[31)] (n = 5), patients with mild renal impairment (n = 12), and patients with moderate or severer renal impairment (n = 8[32)]) were(a) 60.0%, 50.0%, and 75.0%, (b) 40.0%, 16.7%, and 50.0%, (c) 40.0%, 8.3%, and 25.0%, (d) 0%, 8.3%, and 12.5%, and (e) 0%, 8.3%, and 12.5%, respectively. The incidences did not show any clear relationship with renal impairment.

6.2.6 Relationship of exposure with changes of QT/QTc interval

In the global phase I study (Study J101), plasma concentrations of valemetostat at the time of electrocardiography were available in 77 patients, and the data in these patients were analyzed for a relationship of the plasma concentrations of valemetostat with changes in QT interval corrected by Fridericia method (QTcF) from baseline (ΔQTcF) using a liner mixed-effects model. The analysis suggested that ΔQTcF would increase with increasing plasma concentrations of valemetostat, but the upper limit of 90% CI of ΔQTcF at C_{max} (geometric mean, 3,690 ng/mL) in patients orally receiving valemetostat 300 mg, the maximum dose in the clinical study, QD was estimated to be below 10 milliseconds. The incidence of QT interval prolonged in the clinical study and caution about QT interval prolonged based on the concerned incidence are discussed in Section "7.R.3.5 Others."

6.2.7 PPK analysis

The population pharmacokinetic (PPK) analysis was performed using a non-liner mixed-effects model (software, NONMEM Version 7.5) based on PK data of valemetostat (3,162 measuring time points for valemetostat and 1,871 measuring time points for unbound valemetostat, in 174 subjects) obtained from the Japanese phase I studies (Studies J107 and J109), global phase I study (Study J101), foreign phase I

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31) Renal function was classified according to the following criteria: Normal, CrCL ≥90 mL/min; mild impairment, CrCL ≥60 mL/min and <90 mL/min; moderate impairment, CrCL ≥30 mL/min and <60 mL/min; and severe impairment, CrCL <30 mL/min.

32) A total of 7 patients with moderate renal impairment and 1 with severe renal impairment were combined for the analysis.

study (Study U106), and Japanese phase II study (Study J201). The PK of valemetostat was described by a 3-compartment model with the sequential zero-order and first-order absorption process, and PK parameters for transfer and elimination were defined as ones of unbound valemetostat.

In this analysis using the basic model with the effect of α1-acid glycoprotein integrated in the maximum binding to plasma protein, possible covariates of valemetostat for (a) CL/F, (b) apparent volume of distribution (V/F), and (c) bioavailability (F1), respectively, were (a) α1-acid glycoprotein, albumin, age, body weight, CrCL, target patients (healthy adults or patients with cancer), sex, race, concomitant drugs, hepatic function,[30)] country of study, and clinical study (Study U106 or any of the other studies than Study U106); (b) α1-acid glycoprotein, albumin, body weight, and clinical study (Study U106 or any of the other studies than Study U106); and (c) concomitant drugs and α1-acid glycoprotein. As a result of assessment, α1-acid glycoprotein, body weight, target patients (healthy adults or patients with cancer), sex, race, hepatic function,[30)] and clinical study (Study U106 or any of the other studies than Study U106) were identified as a significant covariate for CL/F, body weight and clinical study (Study U106 or any of the other studies than Study U106) for V/F, and α1-acid glycoprotein for F1. The applicant explained that these covariates were all found to have limited effects on the PK parameters of unbound valemetostat and thus are unlikely to cause clinically relevant effects on the PK of unbound valemetostat.

6.2.8 Relationships between exposure and efficacy or safety

6.2.8.1 Relationship between exposure and efficacy

Based on data from the Japanese phase II study (Study J201) and global phase I study (Study J101), relationships between exposure[33)] to unbound valemetostat (steady-state AUC) and the response rate were investigated. The response rate tended to increase with increasing exposure to unbound valemetostat.

6.2.8.2 Relationship between exposure and safety

Based on data from the Japanese phase II study (Study J201) and global phase I study (Study J101), relationships between exposure[33)] to unbound valemetostat (steady-state AUC) and Grade ≥3 platelet count decreased, Grade ≥3 neutrophil count decreased, Grade ≥3 anaemia, adverse events leading to dose reduction, adverse events leading to interruption, and Grade ≥3 adverse events were investigated. The results suggested that incidences of the above adverse events would increase with increasing exposure to unbound valemetostat.

6.2.9 Difference in the PK of valemetostat between Japanese and non-Japanese patients

In the global phase I study (Study J101), no clear differences were observed in PK parameters of valemetostat between Japanese and non-Japanese patients after oral administration of valemetostat 200 mg QD (Table 18). Based on this finding, the applicant explained that no clear differences were observed in the PK of valemetostat between Japanese and non-Japanese patients.

33) Estimated by the PPK analysis [see Section 6.2.7].

Table 18. PK parameters of valemetostat

Day of measurement (Day)	Population	n	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
1	Japanese	30	1,890 (65.5)	3.97 (0.97, 22.90)	14,800 (64.3)[*2]	8.34 (16.2)[*3]
	Non-Japanese	31	1,430 (119.7)	3.83 (0.17, 6.25)	9,620 (128.5)[*4]	9.79 (113.0)[*5]
15	Japanese	28	1,860 (58.7)	3.95 (0.92, 6.05)	16,200 (53.2)[*6]	10.5 (31.0)[*7]
	Non-Japanese	29	1,810 (99.3)	2.30 (0.00, 5.78)	14,200 (97.2)[*8]	9.17 (21.2)[*9]

Geometric mean (CV %); [*1] Median (minimum, maximum); [*2] n = 29; [*3] n = 21; [*4] n = 24; [*5] n = 18; [*6] n = 26; [*7] n = 22; [*8] n = 24; [*9] n = 15

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the applicant's explanation about clinical pharmacology of valemetostat is acceptable except for discussion in the following subsection.

6.R.1 Timing of valemetostat administration

The applicant's explanation about timing of the administration of valemetostat:

Results from the Japanese phase I studies (Studies J103 and J109) suggested that C_{max} and AUC_{inf} of valemetostat after administration in the high-fat-meal- and low-fat-meal-fed state were about 50% and 30% and about 60% and 50%, respectively, lower than those after administration in the fasted state [see Sections 6.1.2.1 and 6.1.2.2]. The Japanese phase II study (Study J201) in which valemetostat was instructed to be administered "at least 1 hour before and 2 hours after a meal" demonstrated the clinical usefulness of valemetostat [see Sections 7.R.2 and 7.R.3].

Considering that valemetostat should be administered in the fasted state based on the above, the applicant will offer clear advice to this effect in the "Dosage and Administration" section, and the "Precautions Concerning Dosage and Administration" section will include a caution against the administration of valemetostat from 1 hour before until 2 hours after a meal [see Section 7.R.5].

PMDA accepted the applicant's explanation.

6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and inducers as well as P-gp inhibitors

The applicant's explanation about concomitant use of valemetostat with CYP3A inhibitors and inducers as well as P-gp inhibitors:

Based on the findings that valemetostat is a substrate of CYP3A4 and P-gp [see Sections 4.3.1 and 4.5.3]; and itraconazole (drug that potently inhibit CYP3A and P-gp), fluconazole (moderate CYP3A inhibitor), or rifampicin (potent CYP3A inducer) concomitantly used had the effect on exposure to valemetostat [see Sections 6.2.3.1 and 6.2.3.2], an analysis was performed for effects of CYP3A inhibitors and inducers as well as P-gp inhibitors on the PK of valemetostat using a physiologically based pharmacokinetic (PBPK) model.

Simcyp simulator version 19 was applied to the PBPK model analysis. For the PK of valemetostat, a full PBPK model accompanied by the advanced dissolution, absorption and metabolism (ADAM) model was selected. Contribution of CYP3A to metabolism of valemetostat was estimated from data in the

Japanese phase I study (Study J104). The effect of P-gp on elimination of valemetostat was integrated in view of results after concomitant use with itraconazole in the Japanese phase I study (Study J104). Physiological parameters and parameters related to fluconazole and rifampicin were defaults of Simcyp, and parameters related to itraconazole's inhibition against P-gp and inhibition constant $(K_i)_{,CYP3A5}$ were values changed from defaults of Simcyp.[34)] Findings described below have supported the appropriateness of the PBPK model used for estimation of pharmacokinetic interactions of valemetostat mediated by CYP3A and P-gp.

- Measured exposure to valemetostat in the Japanese phase I study (Study J103) almost agreed with the estimate obtained in the above PBPK model, and measured and estimated concentrations similarly changed over time.
- Ratios of measured exposure to valemetostat after concomitant use of valemetostat with itraconazole, fluconazole, and rifampicin to that after the administration of valemetostat alone in the Japanese phase I studies (Studies J104 and J107) almost agreed with the estimates obtained in the above PBPK model.
- Ratios of measured exposure to a CYP3A substrate such as midazolam after concomitant use of the concerned substrate with CYP3A inhibitors and inducers to that after administration of the concerned substrate alone (*Clin Pharmacol Ther.* 1994;55:481-5, etc.) almost agreed with the estimates obtained in the above PBPK model.

Analyses using the above PBPK model presented the following estimates:

- Geometric mean ratios of C_{max} and AUC_{inf} of valemetostat after concomitant use of valemetostat with itraconazole (potent CYP3A inhibitor[35)]) and itraconazole (drug that potently inhibits CYP3A and P-gp) to those after the administration of valemetostat alone were estimated to be 2.13 and 2.67, as well as 2.59 and 4.08, respectively.
- Complete inhibition against P-gp-mediated elimination of valemetostat[36)] was estimated to increase C_{max} and $AUC_{0\text{-}96h}$ of valemetostat 1.59 and 2.58 times.
- Geometric mean ratios of C_{max} and AUC_{inf} of valemetostat after concomitant use of valemetostat with efavirenz (moderate CYP3A inducer) to those after the administration of valemetostat alone were 0.666 and 0.575, respectively.

Concerning concomitant use of valemetostat with CYP3A inhibitors and inducers as well as P-gp inhibitors, the following ideas are derived from results in the Japanese phase I studies (Studies J104 and J107) and the above results.

(a) Concomitant use of valemetostat with a drug that potently inhibits CYP3A and P-gp, potent CYP3A inhibitor, or P-gp inhibitor

The geometric mean ratio of AUC_{inf} of valemetostat after concomitant use of valemetostat with itraconazole (drug that potently inhibits CYP3A and P-gp) to that after the administration of valemetostat alone in the Japanese phase I study (Study J104) was 4.19 [see Section 6.2.3.1]. In view of the above

34) The same value was applied to $K_{i,CYP3A5}$ and $K_{i,CYP3A4}$, and parameters related to the inhibition against P-gp were specified based on publication (*Drug Metab Dispos.* 2016;44:453-9, etc.)
35) The estimate was calculated on the assumption that itraconazole potently inhibited CYP3A only.
36) Although the complete inhibition against P-gp-mediated elimination of valemetostat is unlikely to occur in clinical settings, the estimates were calculated based on the above conservative assumption.

and the estimates obtained in the above PBPK model, concomitant use of a drug that potently inhibits CYP3A and P-gp, potent CYP3A inhibitor, or P-gp inhibitor would require the physician to reduce the dose of valemetostat and monitor the patient carefully for adverse drug reactions. In addition, for concomitant use with (i) a drug that potently inhibits CYP3A and P-gp and (ii) a potent CYP3A inhibitor or P-gp inhibitor, the dose of valemetostat should be reduced to (i) a quarter and (ii) half, respectively. In Study J201, the above dose reduction principle was applied, and the dose of valemetostat was reduced to 50 mg in 1 patient concomitantly treated with a drug that potently inhibits CYP3A and P-gp. In this patient, the exposure to valemetostat was comparable to that in patients not concomitantly treated with a P-gp inhibitor or potent CYP3A inhibitor, and no definite concerns about the efficacy or safety were observed. In a foreign phase I study (Study DS3201-A-U102),[37] the exposure approximately twice that after the administration of valemetostat 200 mg was tolerated.

An analysis using the above PBPK model revealed that a plasma concentration profile with the administration of valemetostat at the initial dose, dose prior to the dose-reduction, 3 days after the end of concomitant use with itraconazole (potent CYP3A inhibitor[35]) or clarithromycin (potent CYP3A inhibitor) was not clearly different from that with the administration of valemetostat alone. Based on this finding, the package insert should include a cautionary statement that valemetostat may be administered at the initial dose, dose prior to the dose-reduction, from 3 days after the end of concomitant use of valemetostat with a drug that potently inhibits CYP3A and P-gp, potent CYP3A inhibitor, or P-gp inhibitor.

(b) Concomitant use of moderate CYP3A inhibitors

In view of the results in the Japanese phase I study (Study J104), concomitant use with a moderate CYP3A inhibitor may increase exposure to valemetostat. Caution should be therefore exercised when a moderate CYP3A inhibitor is concomitantly administered.

(c) Concomitant use of moderate or stronger CYP3A inducers

In view of the results in the Japanese phase I study (Study J107) and of the analysis using the above PBPK model, concomitant use with a moderate or potent CYP3A inducer may decrease exposure to valemetostat. Caution should be therefore exercised when a moderate or potent CYP3A inducer is concomitantly administered.

PMDA's review:

PMDA accepted the applicant's explanation about concomitant use of valemetostat with a drug that potently inhibits CYP3A and P-gp as well as moderate or potent CYP3A inhibitors and inducers.

Concerning dose adjustment of valemetostat in use with concomitant P-gp inhibitor, in an analysis using the PBPK model, complete inhibition against P-gp-mediated elimination of valemetostat was estimated to increase $AUC_{0\text{-}96h}$ of valemetostat 2.58 times, but no clinical study results are available on pharmacokinetic interactions of valemetostat with P-gp inhibitors, and the effect of P-gp on elimination of valemetostat has not been adequately investigated. The above estimates on exposure thus remain

[37] A clinical study in patients with acute myeloid leukemia (AML) and acute lymphocytic leukemia to investigate tolerability of QD regimens of valemetostat 100 to 700 mg

uncertain. However, in view that the exposure level approximately twice that after the administration of valemetostat 200 mg was tolerated in the foreign phase I study (Study DS3201-A-U102), safety concerns attributable to the uncertainty in the estimated level of exposure to valemetostat are considered insignificant. Taking also account of the safety risks attributable to increased exposure to valemetostat because of the dose of valemetostat that was not reduced during concomitant use of a P-gp inhibitor, PMDA considers it understandable to a certain extent to advise, for reference, that the dose of valemetostat should be halved for its concomitant use with a P-gp inhibitor. The concerned criteria for dose adjustment should be included in the "Precautions Concerning Dosage and Administration" section in the package insert [see Section 7.R.5].

Meanwhile, after the end of concomitant use of a potent CYP3A and P-gp inhibitor, potent CYP3A inhibitor, or P-gp inhibitor, the determination on the timing of switching back from the reduced dose of valemetostat to the dose before reduction requires the consideration of the half-life, inhibitory potency, the inhibition mode, etc. of each inhibitor. It is therefore difficult to uniformly specify the timing to switch back from the reduced dose of valemetostat to the dose before reduction only based on the estimates with concomitant itraconazole or clarithromycin. The switching timing should not be advised in the package insert.

Information about pharmacokinetic interactions with CYP3A inhibitors and inducers as well as P-gp inhibitors is considered important in supporting the appropriateness of the cautionary advice about concomitant use with CYP3A inhibitors and inducers and P-gp inhibitors based on the estimates obtained from the PBPK model. Information should be further collected, and new findings should be communicated appropriately to healthcare professionals once available.

6.R.3 Pharmacokinetic interactions with CYP3A substrates and P-gp substrates

The applicant's explanation about concomitant use of valemetostat with CYP3A substrates and P-gp substrates:

In the global phase I study in patients with relapsed or refractory NHL (Study J101), the DDI cohort (target sample size, 14 patients to be included in the PK analysis) to investigate the effect of valemetostat on the PK of midazolam (CYP3A substrate) and digoxin (P-gp substrate) is being studied. In this cohort, midazolam 2 mg and digoxin 0.25 mg are orally administered on Days –4 and 15 of Cycle 1, while valemetostat 200 mg is orally administered QD from Days 1 to 28.

A preliminary analysis[38)] in this cohort revealed that least-squares geometric mean ratios [90% CI] of C_{max} and AUC_{last} of midazolam after concomitant use of midazolam with valemetostat to those after administration of midazolam alone were 0.926 [0.726, 1.183] and 0.861 [0.732, 1.013] (n = 15 for both), respectively. The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{last} of digoxin after concomitant use of digoxin with valemetostat to those after administration of digoxin alone were 1.298 [1.074, 1.568] and 1.271 [1.062, 1.522] (n = 16 for both), respectively.

[38)] After all the subjects completed the DDI evaluation period, the interim database was fixed on [redacted], 20[redacted] and was subjected to the preliminary analysis.

Because the above results showed that concomitant use of valemetostat increased exposure to the P-gp substrate, caution should be exercised for concomitant use with a drug potentially acting as a P-gp substrate. The package insert will offer this advice to raise caution. In contrast, concomitant use of valemetostat did not have any clear effect on exposure to a CYP3A substrate, caution about concomitant use with a drug potentially acting as a CYP3A substrate is unnecessary. The final analysis results in the DDI cohort in Study J101 are scheduled to be available in the first quarter of 20[redacted].

PMDA's review:
PMDA largely accepted the applicant's explanation. However, when the final analysis results in the currently ongoing DDI cohort in Study J101 become available, information should be provided appropriately to healthcare professionals.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results from a total of 8 studies including 4 Japanese phase I studies, 1 Japanese phase II study, 1 global phase I study, and 2 foreign phase I studies presented in Table 19.

Table 19. List of clinical studies for efficacy and safety

Data category	Region	Study ID	Phase	Study population	Number of enrollments	Dosage regimen	Major endpoints
Evaluation	Japan	J103	I	Healthy adults	50 (a) 18 (b) 16 (c) 16	Part 1: (a) A single dose of valemetostat 50, 100, or 200 mg was orally administered. Part 2: (b) Group 1: A single dose of valemetostat 200 mg (capsule or tablet) was orally administered. (c) Group 2: A single dose of valemetostat 200 mg was orally administered in the fasted state or high-fat-meal fed state	PK
		J104	I	Healthy adults	32 (a) 16 (b) 16	(a) Group 1: A single dose of valemetostat 25 mg was orally administered on Day 1 followed by a 4-day washout period, and during itraconazole treatment, a single oral administration of valemetostat 25 mg on Day 11. (b) Group 2: A single dose of valemetostat 25 mg was orally administered on Day 1 followed by a 4-day washout period, and during fluconazole treatment, a single oral administration of valemetostat 25 mg on Day 12	PK
		J107	I	Healthy adults	20	A single dose of valemetostat 200 mg was orally administered on Day 1 followed by a 6-day washout period, and during rifampicin treatment, a single oral administration of valemetostat 200 mg on Day 16	PK
		J109	I	Healthy adults	28	A single dose of valemetostat 200 mg was orally administered in the fasted state or low-fat-meal fed state	PK
		J201	II	Patients with relapsed or refractory ATLL	25	Oral QD regimen of valemetostat 200 mg (in the fasted state)	Efficacy Safety
	Global	J101	I	Dose escalation part: Patients with relapsed or refractory NHL Dose expansion part: Patients with relapsed or refractory ATLL and patients with PTCL	(a) 25 (b) 53	(a) Dose escalation part: Oral QD regimen of valemetostat 150-300 mg (in the fasted state) (b) Dose expansion part: Oral QD regimen of valemetostat 200 mg (in the fasted state)	Safety PK
	Foreign	U105	I	Healthy adults	8	A single dose of ^{14}C-valemetostat 200 mg was orally administered	PK
		U106	I	Patients with hepatic impairment	24	A single dose of valemetostat 50 mg was orally administered	PK

Each clinical study is summarized below. The main adverse events other than death observed in each clinical study are described in Section "7.2 Adverse events, etc. observed in clinical studies" and results of clinical studies for PK in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology

The applicant submitted results of the following 6 clinical pharmacological studies in healthy adults and patients with hepatic impairment [see Sections 6.1 and 6.2]. No deaths occurred during the valemetostat treatment or follow-up period[39] in these studies.

7.1.1.1 Japanese phase I study (CTD 5.3.1.1-1, Study J103, [redacted] to [redacted])

7.1.1.2 Japanese phase I study (CTD 5.3.3.4-1, Study J104, [redacted] to [redacted])

7.1.1.3 Japanese phase I study (CTD 5.3.3.4-2, Study J107, July to [redacted] 2020)

7.1.1.4 Japanese phase I study (CTD 5.3.1.1-2, Study J109, October 2020 to January 2021)

7.1.1.5 Foreign phase I study (CTD 5.3.3.1-1, Study U105, [redacted] to [redacted])

7.1.1.6 Foreign phase I study (CTD 5.3.3.3-1, Study U106, January 2020 to February 2021)

7.1.2 Japanese clinical study

7.1.2.1 Japanese phase II study (CTD 5.3.5.2-1, Study J201, ongoing since November 2019 [data cut-off on April 24, 2021])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory ATLL[40] (target sample size, 25 subjects) to investigate the efficacy and safety of valemetostat at 24 study sites in Japan.

Valemetostat 200 mg was orally administered in the fasted state[41] QD until the criteria for treatment discontinuation were met.

All of 25 patients enrolled in the study received valemetostat and were included in the efficacy[42] and safety analysis populations.

The primary endpoint of the study was specified as the response rate based on central assessment according to the partially modified version of the criteria of the International Conference on Human Retrovirology (*J Clin Oncol.* 2009;27:453-9) (Table 20).

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39) The follow-up period after the study drug treatment was 7 days for Part 1 and 7 to 9 days for Part 2 in Study J103; 4 days after the administration of valemetostat alone and 13 to 15 days after concomitant use of valemetostat with itraconazole or fluconazole in Study J104; 6 days after the administration of valemetostat alone and 13 to 15 days after concomitant use of valemetostat with rifampicin in Study J107; 7 to 9 days in Study J109; 30 days in Study U105; and 8 days in Study U106.

40) Patients with relapsed or refractory ATLL which was classified into the acute type, lymphoma type, or chronic type with unfavorable prognostic factors and who had previously received mogamulizumab or had been intolerant of or ineligible for mogamulizumab and thus had received at least 1 regimen of systemic chemotherapy were included.

41) Administered ≥1 hour before or ≥2 hours after a meal

42) The primary efficacy analysis population was defined as the population of patients who received at least 1 dose of the study drug and in whom any of (a) complete response (CR), complete response unconfirmed (CRu), or partial response (PR) was centrally assessed; (b) the study drug treatment was discontinued; or (c) central antitumor effect determination on Day 1 of Cycle 7 was completed was met. The first data cut-off was scheduled on the day when 21 patients were included in the primary efficacy analysis population in the order of enrollment.

Table 20. Modified version of the criteria of the International Conference on Human Retrovirology

Overall response	Target lesion		Non-target lesion		Splenomegaly, hepatomegaly	Skin lesion (mSWAT)[*1]	Peripheral blood image	Bone marrow infiltration
	Nodal	Extranodal	Nodal	Extranodal				
CR[*2]	Normal	Disappearance	Normal	Disappearance	Normal	Normal	Abnormal lymphocytes <5% of white blood cells, lymphocyte count <4000/μL	Normal
CRu[*2]	≥75% reduction in size		Normal	Disappearance	Normal	Normal	Same as above	Normal
PR[*2]	≥50% reduction in size		Normal or no increase in size	Disappearance or no increase in size	No increase in size	≥50% decrease	≥50% decrease	Irrelevant
SD[*2]	<50% reduction in size or <50% increase in size		No CR, PR, or PD		No change	No change	No change	No change
RD/PD	New appearance or ≥50% increase in size		Increase in size or re-swelling	Increase in size or reappearance	New appearance or ≥50% increase	≥50% increase	New appearance or ≥50% increase from nadir and lymphocyte count ≥4000/μL	Reappearance

*[1] The skin lesion was assessed according to the modified Severity Weighted Assessment Tool (mSWAT) (*J Clin Oncol.* 2007;25:3109-15)
*[2] Not required to confirm the presence for at least 4 weeks

Table 21 shows the response rate[43)] based on central assessment according to the modified version of the criteria of the International Conference on Human Retrovirology.

Table 21. Best overall response and response rate (central assessment, efficacy analysis population, data cut-off on April 24, 2021)

Best overall response	Number of patients (%) n = 25
CR	5 (20.0)
CRu	0
PR	7 (28.0)
SD	10 (40.0)
RD/PD	3 (12.0)
Response (CR, CRu, or PR) (response rate [95% CI][*1] [%])	12 (48.0 [27.8, 68.7])
P value[*2]	<0.0001

*[1] Clopper-Pearson method; *[2] Binomial test with the threshold response rate of 5%, one-sided significance level of 0.05

The centrally assessed response rate [95% CI] (%) in patients with relapsed[44)] ATLL was 50.0 [23.0, 77.0] (7 of 14 patients), and that in patients with refractory[45)] ATLL was 45.5 [16.7, 76.6] (5 of 11 patients).

No deaths occurred during the valemetostat treatment or within 35 days after the end of the treatment.

43) In view that the standard therapy for relapsed or refractory ATLL has not been established, the threshold of the response rate was specified as 5%.
44) Patients who attained PR or better response to the last treatment
45) Patients who had stable disease (SD) or worse response to the last treatment

7.1.3 Global study

7.1.3.1 Global phase I study (CTD 5.3.3.2-1, Study J101, ongoing since March 2016 [data cut-off on November 2, 2020])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory NHL (maximum target sample size, 27 subjects in dose escalation part) and patients with relapsed or refractory ATLL and patients with PTCL (maximum target sample size, 10 subjects in ATLL cohort, 50 subjects in PTCL cohort in dose expansion part[46]) to investigate the safety of valemetostat at 14 study sites in the 2 countries of Japan and the US.

Valemetostat was orally administered in the fasted state[41] QD at 150, 200, 250, and 300 mg in the dose escalation part and then 200 mg in the dose expansion part, and the treatment was continued until the criteria for treatment discontinuation were met.

All of 78 patients enrolled in the study (25 in the dose escalation part [7 in the 150 mg cohort, 9 in the 200 mg cohort, 7 in the 250 mg cohort, 2 in the 300 mg cohort]; 53 in the dose expansion part) received valemetostat and 77 patients excluding 1 patient in the dose expansion part[47] were included in the safety analysis population. Of the safety analysis population, 25 patients in the dose escalation part were included in the dose limiting toxicity (DLT) evaluation.

During a period of 28 days after the first dose of valemetostat, the DLT evaluation period, DLT was observed in 1 of 9 patients in the 200 mg cohort (Grade 4 platelet count decreased in 1 patient) and 2 of 2 patients in the 300 mg cohort (Grade 3 anaemia/Grade 4 platelet counts decreased in 1 patient and Grade 4 platelet count decreased in 1 patient), and valemetostat 200 mg was specified as the recommended dose.

No deaths occurred during the valemetostat treatment or within 35 days after the end of the treatment.[48]

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA determined that, among the evaluation data submitted, the pivotal study for evaluation of the efficacy and safety of valemetostat was the Japanese phase II study (Study J201) in patients with relapsed or refractory ATLL, and decided to evaluate the submitted data focusing on this study.

7.R.2 Efficacy

Based on the following review, PMDA has concluded that valemetostat had been demonstrated to have efficacy in patients with relapsed or refractory ATLL to a certain extent.

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[46] The maximum sample sizes of 10 patients with ATLL and 50 patients with PTCL include patients enrolled in the dose escalation part.
[47] The patient received valemetostat 200 mg but was excluded from the analysis population owing to violation of the GCP in obtaining consent.
[48] The patient excluded from the analysis population in the dose expansion part owing to the GCP violation died of disease progression 22 days after the last dose of valemetostat.

7.R.2.1 Efficacy endpoints and evaluation results

In Study J201, the response rate based on central assessment according to the modified version of the criteria of the International Conference on Human Retrovirology, defined as the primary endpoint, met the pre-determined efficacy criteria [see Section 7.1.2.1].

Figure 1 shows the maximum percent change in total tumor size (sum of bidimensional products) of the nodal/extranodal target lesions in patients with evaluable lesions at baseline. The median duration of the centrally assessed response [95% CI] (months), defined as the secondary endpoint, was not estimated [1.87, not estimated].[49)]

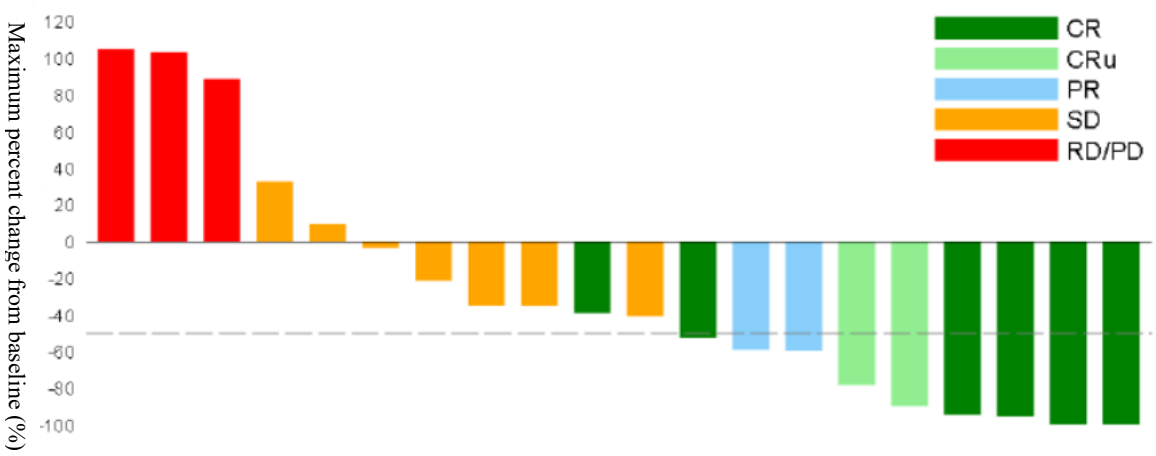

Figure 1. Maximum percent change in total tumor size (sum of the product of the diameters) of nodal/extranodal target lesions
(modified version of the criteria of the International Conference on Human Retrovirology, central assessment, efficacy analysis population)

The response rate [95% CI] (%) according to the modified version of the criteria of the International Conference on Human Retrovirology in patients with ATLL enrolled in Study J201 by disease type was 62.5 [35.4, 84.8] (10 of 16 patients) for the acute type, 16.7 [0.4, 64.1] (1 of 6 patients) for lymphoma type, and 33.3 [0.8, 90.6] (1 of 3 patients) for the chronic type with unfavorable prognostic factors.[50)]

The applicant's explanation about the response rate, the primary endpoint in Study J201:
Outcome in patients with relapsed or refractory ATLL is poor, and no standard therapy demonstrated to extend overall survival (OS) has been established. ATLL is accompanied by serious disease-related symptoms such as general lymph node swelling and skin lesions, which adversely affect the quality of life of the patient (Practical Guidelines for Hematological Malignancies 2018, Enlarged edition, by the Japanese Society of Hematology). The response in such patients represents reduction in tumor volume, which is expected to alleviate the accompanying symptoms and delay the start of the next treatment, and is therefore considered clinically meaningful.

[49)] The duration of response ranged from 1.18 to 11.99 months (censored because of continued response).
[50)] Any of the following laboratory values was met: Serum albumin below the lower limit of normal; lactate dehydrogenase (LDH) exceeded the upper limit of normal; and blood urea nitrogen (BUN) exceeded the upper limit of normal.

PMDA's review:
The applicant's explanation about the efficacy endpoint is understandable. Based on the above results, valemetostat is demonstrated to have efficacy in patients with relapsed or refractory ATLL to a certain extent. Data on the efficacy by disease type should be appropriately provided to healthcare professionals using a proper use guide, etc.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events, etc. observed in clinical studies"]

PMDA's view:
Based on the following review, adverse events requiring particular attention in treatment with valemetostat are myelosuppression, infections, and secondary malignant tumor. These events warrant attention during the use of valemetostat.

Although the above adverse events warrant attention during the treatment, valemetostat will be tolerable when appropriate measures, such as monitoring and controlling of adverse events and interruption, dose reduction, and discontinuation of valemetostat, are taken by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy. However, safety information should be further collected in post-marketing settings because of extremely limited treatment experience with valemetostat [see Section 7.R.6].

7.R.3.1 Safety profile of valemetostat and difference in safety between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of valemetostat based on the safety information in the population treated with valemetostat 200 mg, the proposed dosage regimen, in Studies J201 and J101:
Table 22 shows the outline of the safety in the population treated with valemetostat 200 mg in Studies J201 and J101.

Table 22. Outline of safety (population treated with valemetostat 200 mg in Studies J201 and J101)

	Number of patients (%)	
	Study J201 n = 25	Population treated with valemetostat 200 mg in Study J101 n = 61
All adverse events	25 (100)	61 (100)
Events for which a causal relationship to valemetostat could not be ruled out	24 (96.0)	51 (83.6)
Grade ≥3 adverse events	15 (60.0)	41 (67.2)
Adverse events resulting in death	0	0
Serious adverse events	8 (32.0)	20 (32.8)
Adverse events leading to treatment discontinuation	2 (8.0)	1 (1.6)
Adverse events leading to interruption	5 (20.0)	27 (44.3)
Adverse events leading to dose reduction	2 (8.0)	4 (6.6)

Table 23 shows all-grade adverse events with an incidence of ≥20% in either Study J201 or the population treated with valemetostat 200 mg in Study J101.

Table 23. Adverse events with an incidence of ≥20% in either study (Study J201 and population treated with valemetostat 200 mg in Study J101)

SOC PT (MedDRA/J ver.23.1)	Number of patients (%)			
	Study J201 n = 25		Population treated with valemetostat 200 mg in Study J101 n = 61	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	25 (100)	15 (60.0)	61 (100)	41 (67.2)
Blood and lymphatic system disorders				
Anaemia	12 (48.0)	8 (32.0)	23 (37.7)	6 (9.8)
Gastrointestinal disorders				
Diarrhoea	2 (8.0)	1 (4.0)	17 (27.9)	0
Nausea	2 (8.0)	0	14 (23.0)	0
General disorders and administration site conditions				
Pyrexia	5 (20.0)	0	8 (13.1)	0
Investigations				
Platelet count decreased	20 (80.0)	8 (32.0)	33 (54.1)	8 (13.1)
Neutrophil count decreased	7 (28.0)	3 (12.0)	20 (32.8)	14 (23.0)
Lymphocyte count decreased	6 (24.0)	4 (16.0)	11 (18.0)	10 (16.4)
White blood cell count decreased	5 (20.0)	3 (12.0)	16 (26.2)	9 (14.8)
Nervous system disorders				
Dysgeusia	9 (36.0)	0	29 (47.5)	0
Skin and subcutaneous tissue disorders				
Alopecia	10 (40.0)	0	19 (31.1)	0
Metabolism and nutrition disorders				
Decreased appetite	5 (20.0)	2 (8.0)	8 (13.1)	0

Serious adverse events in Study J201 were cytomegalovirus chorioretinitis, cytomegalovirus infection reactivation, pneumonia, febrile neutropenia, hypercalcaemia, cardiac failure, venous thrombosis limb, lower gastrointestinal haemorrhage, hepatic function abnormal, acute kidney injury, platelet count decreased, and overdose in 1 patient (4.0%) each (some patients experienced multiple events), and a causal relationship to valemetostat could not be ruled out for all the above events except for hypercalcaemia and overdose. Adverse events leading to discontinuation of valemetostat were cardiac failure and platelet count decreased in 1 patient (4.0%) each, and a causal relationship to valemetostat could not be ruled out for either event. Adverse events leading to interruption of valemetostat reported in ≥2 patients were febrile neutropenia and platelet count decreased in 2 patients (8.0%) each. There were neither adverse events leading to death nor dose reduction of valemetostat reported in ≥2 patients.

Serious adverse events reported in ≥2 patients in the population treated with valemetostat 200 mg in Study J101 were *Pneumocystis jirovecii* pneumonia, cytomegalovirus infection, tumour associated fever, febrile neutropenia, hypercalcaemia, and pyrexia in 2 patients (3.3%) each, and a causal relationship to valemetostat could not be ruled out for *Pneumocystis jirovecii* pneumonia and cytomegalovirus infection in 2 patients each and febrile neutropenia in 1 patient. Adverse events leading to interruption of valemetostat reported in ≥2 patients were dysgeusia in 4 patients (6.6%), cytomegalovirus infection, neutrophil count decreased, and platelet count decreased in 3 patients (4.9%) each, and decreased appetite, pneumonitis, fatigue, and malaise in 2 patients (3.3%) each. An adverse event leading to dose reduction of valemetostat reported in ≥2 patients was platelet count decreased in 2 patients (3.3%). There were neither adverse events leading to death nor adverse events leading to discontinuation of valemetostat reported in ≥2 patients.

In the population treated with valemetostat 200 mg in Study J101, all-grade adverse events of which the incidence was ≥20% higher in the Japanese sub-group than the non-Japanese sub-group were platelet count decreased (25 Japanese patients [83.3%], 8 non-Japanese patients [25.8%]), white blood cell count decreased (14 patients [46.7%], 2 patients [6.5%]), lymphocyte count decreased (10 patients [33.3%], 1 patient [3.2%]), neutrophil count decreased (14 patients [46.7%], 6 patients [19.4%]), alanine aminotransferase (ALT) increased (10 patients [33.3%], 2 patients [6.5%]), nasopharyngitis (6 patients [20.0%], 0 patients), and rash (6 patients [20.0%], 0 patients). Grade ≥3 adverse events of which the incidence was ≥10% higher in the Japanese patients than in the non-Japanese patients were lymphocyte count decreased (9 patients [30.0%], 1 patient [3.2%]), white blood cell count decreased (7 patients [23.3%], 2 patients [6.5%]), neutrophil count decreased (9 patients [30.0%], 5 patients [16.1%]), and gamma-glutamyltransferase (GGT) increased (3 patients [10.0%], 0 patients). Serious adverse events of which the incidence was ≥5% higher in the Japanese patients than in the non-Japanese patients were *Pneumocystis jirovecii* pneumonia (2 patients [6.7%], 0 patients), cytomegalovirus infection (2 patients [6.7%], 0 patients), tumour associated fever (2 patients [6.7%], 0 patients), and pyrexia (2 patients [6.7%], 0 patients). An adverse event leading to interruption of valemetostat of which the incidence was ≥10% higher in the Japanese patients than in the non-Japanese patients was cytomegalovirus infection (3 patients [10.0%], 0 patients). There were neither adverse events leading to discontinuation nor dose reduction of valemetostat of which the incidence was ≥10% higher in the Japanese patients than in the non-Japanese patients.

PMDA's review:
The serious adverse events, Grade ≥3 adverse events, and adverse events leading to discontinuation of valemetostat in Study J201 and the population treated with valemetostat 200 mg in Study J101 require special attention during use of valemetostat; and the occurrence of these events should be appropriately communicated to healthcare professionals using the package insert, etc.

In the following sections, PMDA mainly reviewed results on the safety in Study J201 with the focus on myelosuppression and infections, the serious adverse events reported in ≥2 patients and for which a causal relationship to valemetostat could not be ruled out, and secondary malignant tumor, which is considered related to the toxicological finding (lymphoma) indicative of a potential safety concern in clinical use; and reviewed the occurrence of serious adverse events and Grade ≥3 adverse events in Study J101.

7.R.3.2 Myelosuppression

The applicant's explanation about myelosuppression associated with valemetostat:
Adverse events of preferred terms (PTs) classified into "Haematopoietic cytopenias (broad)," a Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ), were compiled as myelosuppression-related events.

Table 24 shows the incidences of myelosuppression in Study J201.

Table 24. Incidences of myelosuppression reported in ≥2 patients (Study J201)

PT (MedDRA/J ver.23.1)	Number of patients (%) n = 25	
	All grades	Grade ≥3
Myelosuppression	21 (84.0)	13 (52.0)
Platelet count decreased	20 (80.0)	8 (32.0)
Anaemia	12 (48.0)	8 (32.0)
Neutrophil count decreased	7 (28.0)	3 (12.0)
Lymphocyte count decreased	6 (24.0)	4 (16.0)
White blood cell count decreased	5 (20.0)	3 (12.0)
Febrile neutropenia	2 (8.0)	2 (8.0)

In Study J201, serious myelosuppression occurred in 2 patients (8.0%, platelet count decreased and febrile neutropenia in 1 patient each), and a causal relationship to valemetostat could not be ruled out for either event. A myelosuppression leading to discontinuation of valemetostat occurred in 1 patient (4.0%), and myelosuppression leading to interruption occurred in 4 patients (16.0%). There were neither fatal myelosuppression nor myelosuppression leading to dose reduction of valemetostat.

In the population treated with valemetostat 200 mg in Study J101, Grade ≥3 myelosuppression occurred in 30 patients (49.2%, events reported in ≥2 patients were neutrophil count decreased in 14 patients, lymphocyte count decreased in 10 patients, white blood cell count decreased in 9 patients, platelet count decreased in 8 patients, anaemia in 6 patients, febrile neutropenia in 3 patients, and thrombocytopenia in 2 patients [some patients experienced multiple events]). Serious myelosuppression occurred in 3 patients (4.9%, febrile neutropenia in 2 patients, thrombocytopenia in 1 patient), and a causal relationship to valemetostat could not be ruled out for febrile neutropenia in 1 patient. No fatal myelosuppression occurred.

PMDA's review:
Myelosuppression warrants attention during the use of valemetostat in view of (a) high incidences of Grade ≥3 myelosuppression associated with valemetostat and (b) serious myelosuppression for which a causal relationship to valemetostat could not be ruled out observed in the clinical studies. Therefore, the applicant is required to inform healthcare professionals of the occurrence of myelosuppression in the clinical studies and advise via the package insert, etc. that hematology tests should be periodically performed during the treatment with valemetostat, and dose interruption or reduction, discontinuation of valemetostat or other measures should be taken in case of abnormality.

7.R.3.3 Infections

The applicant's explanation about infections associated with valemetostat:
Adverse events of PTs classified into "Infections and infestations," a system organ class (SOC) of MedDRA, were tabulated as infection-related events.

Table 25 shows incidences of infection in Study J201.

Table 25. Incidences of infection (Study J201)

PT (MedDRA/J ver.23.1)	Number of patients (%) n = 25	
	All grades	Grade ≥3
Infections	9 (36.0)	3 (12.0)
Cytomegalovirus infection reactivation	3 (12.0)	2 (8.0)
Cytomegalovirus viraemia	2 (8.0)	0
Conjunctivitis	1 (4.0)	0
Cytomegalovirus chorioretinitis	1 (4.0)	1 (4.0)
Furuncle	1 (4.0)	0
Nasopharyngitis	1 (4.0)	0
Oral herpes	1 (4.0)	0
Pneumonia	1 (4.0)	1 (4.0)
Tinea cruris	1 (4.0)	0

In Study J201, serious infection occurred in 2 patients (8.0%, cytomegalovirus infection reactivation, cytomegalovirus chorioretinitis, and pneumonia in 1 patient each [some patients experienced multiple events]), and a causal relationship to valemetostat could not be ruled out for all the events. Infection leading to interruption of valemetostat occurred in 1 patient (4.0%). There was no fatal infection, or infection leading to discontinuation or dose reduction of valemetostat.

In the population treated with valemetostat 200 mg in Study J101, Grade ≥3 infection occurred in 8 patients (13.1%, *Pneumocystis jirovecii* pneumonia and cytomegalovirus infection in 2 patients each, cytomegalovirus chorioretinitis, epiglottitis, infection, sepsis, and streptococcal bacteraemia in 1 patient each [some patients experienced multiple events]). Serious infection occurred in 6 patients (9.8%, *Pneumocystis jirovecii* pneumonia and cytomegalovirus infection in 2 patients each, cytomegalovirus chorioretinitis, epiglottitis, and infection in 1 patient each [some patients experienced multiple events]), and a causal relationship to valemetostat could not be ruled out for *Pneumocystis jirovecii* pneumonia and cytomegalovirus infection in 2 patients each and infection in 1 patient. No fatal infection occurred.

PMDA asked the applicant about (a) screening and the monitoring status of opportunistic infection (including viral reactivation) and hepatitis B virus (HBV) infection and (b) incidences of opportunistic infection and HBV infection and the status of prophylactic administration in Study J201.

The applicant's response:
(a) There is no specification on screening or monitoring for opportunistic infection. In terms of HBV infection, patients positive for HBs antigen (hepatitis B surface antigen) and patients positive for HBs antibody (anti-hepatitis B surface antigen) or HBc antibody (anti-hepatitis B core antigen) and quantitatively positive for HBV-DNA (≥2.1 log copies/mL) were excluded. Patients positive for HBs antibody or HBc antibody but quantitatively non-positive for HBV-DNA were allowed to be enrolled in the study and required to be monitored for HBV-DNA every 1 to 3 months.

(b) The protocol recommends prophylactic medication using a sulfamethoxazole-trimethoprim combination product, etc. against *Pneumocystis jirovecii* but did not specify prophylactic medication against the other opportunistic infections. The following describe opportunistic infections and HBV infection observed and the status of prophylactic medication in Study J201.

- Against cytomegalovirus (CMV) infection,[51] no prophylactic medication was provided. CMV infection occurred in 5 of 25 patients (20.0%).
- Against *Mycobacterium tuberculosis* infection,[52] 3 of 25 patients (12.0%) received prophylactic medication. No *Mycobacterium tuberculosis* infection occurred irrespective of the status of prophylactic medication.
- Against *Pneumocystis jirovecii* infection,[53] 19 of 25 patients (76.0%) received prophylactic medication. No *Pneumocystis jirovecii* infection occurred irrespective of the status of prophylactic medication.
- Against varicella zoster virus (VZV) infection,[54] 15 of 25 patients (60.0%) received prophylactic medication. No VZV infections occurred irrespective of the status of prophylactic medication.
- Against HBV infection,[55] no prophylactic medication was provided. No HBV infections occurred.

PMDA's review:
In view of the occurrence of serious infections (including opportunistic infections) for which a causal relationship to valemetostat could not be ruled out in ≥2 patients in the clinical studies, infections warrant attention during the treatment with valemetostat. Therefore, healthcare professionals should be appropriately informed of the occurrence of infections including opportunistic infections in the clinical studies via the package insert, etc. and of the safety measures actually taken in the clinical studies such as prophylactic medication against infections, via separate materials.

7.R.3.4 Secondary malignant tumor

The applicant's explanation about secondary malignant tumors associated with valemetostat:
Adverse events of PTs classified into "Malignant tumours (narrow)," an SMQ of MedDRA, were tabulated as secondary malignant tumor-related events.

In Study J201, no secondary malignant tumor occurred.

In the population treated with valemetostat 200 mg in Study J101, Grade ≥3 secondary malignant tumor occurred in 1 patient (1.6%, chronic myelomonocytic leukaemia).[56] Serious secondary malignant tumor occurred in 1 patient (1.6%, chronic myelomonocytic leukaemia), and the causal relationship to valemetostat could not be ruled out. Fatal secondary malignant tumor occurred in 1 patient (1.6%, chronic myelomonocytic leukaemia), and the causal relationship to valemetostat could not be ruled out.

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51) Adverse events of PTs classified into "Cytomegalovirus infection," a high level term (HLT) of MedDRA, were compiled.
52) Adverse events of PTs classified into "Tuberculous infections," an HLT of MedDRA, were compiled.
53) Adverse events of PTs classified into "Pneumocystis infections," an HLT of MedDRA, were compiled.
54) Adverse events reported as the following PTs of MedDRA were compiled: "Varicella," "Herpes zoster oticus," "Herpes zoster," "Ophthalmic herpes zoster," "Herpes zoster infection neurological," "Herpes zoster meningitis," "*Varicella zoster* pneumonia," "*Varicella zoster virus* infection," "Herpes zoster cutaneous disseminated," "Disseminated *varicella zoster virus* infection," "Varicella post vaccine," "Genital herpes zoster," "Varicella zoster gastritis," "Varicella zoster oesophagitis," "Herpes zoster pharyngitis," "Herpes zoster meningoencephalitis," "Herpes zoster meningomyelitis," "Herpes zoster necrotising retinopathy," "Varicella zoster sepsis," "Disseminated varicella zoster vaccine virus infection," "Varicella keratitis," "Haemorrhagic varicella syndrome," "Herpes zoster meningoradiculitis", "Herpes zoster reactivation," and "Disseminated varicella."
55) Adverse events of PTs classified into "Hepatitis virus infections," an HLT of MedDRA, and related to type B were compiled.
56) The event of chronic myelomonocytic leukaemia in the population treated with valemetostat 200 mg in Study J101 was reported after data cut-off (November 2, 2020).

In addition, precursor B-cell leukemia was reported in an investigator-initiated study of valemetostat in pediatric patients with malignant tumors, which is not included in the clinical study data submitted for this application.[57)]

PMDA's review:
Because secondary malignant tumor occurred only in the limited number of patients in the clinical studies, it is therefore difficult to draw a definite conclusion about a relationship between the secondary malignant tumor and valemetostat at present. However, in view of the occurrence of (a) serious secondary malignant tumor for which a causal relationship to valemetostat could not be ruled out in the clinical studies and (b) lymphoma in the non-clinical study [see Section 5.R.1], secondary malignant tumor warrants attention during the use of valemetostat. The applicant is therefore required to provide information about the occurrence of secondary malignant tumor in the clinical studies via the package insert, etc. while continuing to collect information in post-marketing settings as well.

7.R.3.5 Others

The applicant's explanation about cardiac disorders (including QT interval prolonged) associated with valemetostat, taking account of QT interval prolongation observed in the repeated-dose toxicity study in dogs [see Section 3.2.2.2]:
Adverse events of PTs classified into "Cardiac disorders," an SOC of MedDRA, and "Torsade de pointes/QT prolongation (narrow)," an SMQ of MedDRA, were tabulated as events related to cardiac disorder (including QT interval prolonged).

Table 26 shows incidences of cardiac disorder (including QT interval prolonged) in Study J201.

Table 26. Incidences of cardiac disorder (including QT interval prolonged) (Study J201)

PT (MedDRA/J ver.23.1)	Number of patients (%) n = 25	
	All grades	Grade ≥3
Cardiac disorders	2 (8.0)	1 (4.0)
Cardiac failure	1 (4.0)	1 (4.0)
Electrocardiogram QT prolonged	1 (4.0)	0

In Study J201, serious cardiac disorder (including QT interval prolonged) occurred in 1 patient (4.0%, cardiac failure), and the causal relationship to valemetostat could not be ruled out. A cardiac disorder (including QT interval prolonged) leading to discontinuation of valemetostat occurred in 1 patient (4.0%). There was no fatal cardiac disorder (including QT interval prolonged), or cardiac disorder (including QT interval prolonged) leading to interruption or dose reduction of valemetostat.

In the population treated with valemetostat 200 mg in Study J101, Grade ≥3 cardiac disorder (including QT interval prolonged) occurred in 2 patients (3.3%, atrial fibrillation, cardiac failure acute, and coronary artery disease in 1 patient each [some patients experienced multiple events]). Serious cardiac disorder (including QT interval prolonged) occurred in 2 patients (3.3%, atrial fibrillation, cardiac failure

[57)] A [redacted]-year old Japanese pediatric female patient with neuroblastoma. The patient experienced precursor B-cell leukemia about 7 months after the start of valemetostat treatment. The concerned event was assessed as serious, and the valemetostat treatment was discontinued. The investigator reported prior chemotherapy with alkylating agents and radiation therapy, genetic predisposition, and valemetostat as potential causes of the concerned event.

acute, and cardiomyopathy in 1 each [some patients experienced multiple events]), and a causal relationship to valemetostat was ruled out for all the events. No fatal cardiac disorder (including QT interval prolonged) occurred.

Table 27 shows changes in QTcF in patients with QTcF measured in Study J201.

Table 27. Changes in QTcF in patients with QTcF measured (Study J201)

	Number of patients (%)
	n = 25
Maximum	
≤450 milliseconds	19 (76.0)
>450 and ≤480 milliseconds	6 (24.0)
>480 and ≤500 milliseconds	0
>500 milliseconds	0
Increase from baseline (maximum)	
<0 milliseconds	2 (8.0)
≥0 and ≤30 milliseconds	20 (80.0)
>30 and ≤60 milliseconds	3 (12.0)
>60 milliseconds	0

PMDA's review:
In view of (a) the limited number of patients experiencing prolonged QT interval in the clinical studies and (b) no clear effect of valemetostat on QTcF, it is difficult to draw a definite conclusion about a risk of prolonged QT interval in patients with relapsed or refractory ATLL receiving valemetostat. The applicant should continue monitoring for the event in post-marketing settings and appropriately update healthcare professionals with new findings whenever available.

7.R.4 Clinical positioning and indication

The proposed indication of valemetostat was "relapsed or refractory adult T-cell leukemia-lymphoma." The "Precautions Concerning Indication" section was proposed to include the following statement:

- Physicians should be well-versed in the information presented in the "Clinical Studies" section, including the disease types of the patients enrolled in the clinical studies and the presence or absence of poor prognostic factors in these patients, and have full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

As a result of the discussion in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsection, PMDA has concluded that the proposed Indication and Precautions Concerning Indication are appropriate.

7.R.4.1 Clinical positioning and indication of valemetostat

Japanese and foreign clinical practice guidelines[58)] or representative textbooks[59)] on hematology were found to have no descriptions about use of valemetostat in patients with relapsed or refractory ATLL.

58) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in T-Cell Lymphomas (NCCN Guidelines) (v.2.2022) and Practical Guidelines for Hematological Malignancies 2018, Enlarged edition, by the Japanese Society of Hematology
59) Wintrobe's Clinical Hematology, 14th Edition (USA: Lippincott Williams & Wilkins, 2018), Williams Hematology, 9th Edition (USA: The McGraw-Hill Company, Inc, 2016)

The applicant's explanation about clinical positioning of valemetostat in treatment of relapsed or refractory ATLL and the indication:

(a) Disease types:

ATLL is classified into 4 clinical disease types, acute, lymphoma, chronic, and smoldering types. The acute type, lymphoma type, and chronic type with unfavorable prognostic factors[50)] are categorized as aggressive ATLL. Multiple-drug therapy is indicated for patients with aggressive ATLL, but there is no established standard therapy shown to improve OS, and these patients have poor prognosis (Practical Guidelines for Hematological Malignancies 2018, Enlarged edition, by the Japanese Society of Hematology). In such situation, Study J201 in patients with relapsed or refractory aggressive ATLL demonstrated the clinical usefulness of valemetostat [see Sections 7.R.2 and 7.R.3], and valemetostat is considered as one of the treatment options for this patient population.

In addition, in view of the following points, valemetostat may be used in patients with ATLL of the smoldering type and chronic type who have no unfavorable prognostic factors, the population excluded from Study J201.

- For treatment-naïve ATLL of the smoldering type or chronic type with no unfavorable prognostic factors, follow-up without therapy or topical skin therapy is recommended. However, once blast crisis occurs, these types are also recommended to be treated as per ATLL of the acute type, lymphoma type, or chronic type with unfavorable prognostic factors. For progressing smoldering type or chronic type with no unfavorable prognostic factors despite such treatment, clinical care for the acute type, lymphoma type, or chronic type with unfavorable prognostic factors is also recommended (Practical Guidelines for Hematological Malignancies 2018, Enlarged edition, by the Japanese Society of Hematology).

(b) Prior treatment

Valemetostat is recommended for the target patient population of Study J201, which demonstrated the clinical usefulness of valemetostat in patients with relapsed or refractory ATLL who had previously received mogamulizumab (genetical recombination) (mogamulizumab) or had been intolerant of or ineligible for mogamulizumab and thus had received at least 1 regimen of systemic chemotherapy.

The patient population that had not received mogamulizumab despite being eligible were excluded from Study J201, and thus have never been treated with valemetostat. However, in Study J201, the patient who had never received mogamulizumab due to ineligibility responded to valemetostat (1 of 1 patient), showing that valemetostat can also be indicated for the patient population excluded from Study J201.

In light of the discussion in above (a) and (b), the applicant proposed the indication of valemetostat as "relapsed or refractory adult T-cell leukemia-lymphoma," while providing patient characteristics of Study J201, including disease types, the presence or absence of unfavorable prognostic factors, etc. in the "Clinical Studies" section and the cautionary note described below in the "Precautions Concerning Indication" section in the package insert.

A definite conclusion on the choice between valemetostat and approved drugs for relapsed or refractory ATLL in Japan, i.e., mogamulizumab, lenalidomide hydrate (lenalidomide), and tucidinostat, is

precluded because of no clinical study data comparing clinical benefits of valemetostat with these antineoplastic agents. Healthcare professionals are thus expected to choose the appropriate one based on the efficacy and safety of each drug and according to the condition of each patient.

- Physicians should be well-versed in the information presented in the "Clinical Studies" section, including the disease types of the patients enrolled in the clinical studies and the presence or absence of poor prognostic factors in these patients, and have full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

PMDA's review:

The efficacy and safety of valemetostat remain unclear in patients with relapsed or refractory ATLL who fall outside the target patient population of Study J201, and there is no adequate evidence that encourages the use of valemetostat in this population. Nevertheless, in view of the following points and the above applicant's explanation, the "Indication" and "Precautions Concerning Indication" sections should be described as proposed.

- The standard therapy for relapsed or refractory ATLL has not been established, and available treatment options are limited.
- Valemetostat is a drug to be used by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy, and eligibility for valemetostat is expected to be appropriately assessed with specific condition of each patient taken into consideration.

7.R.5 Dosage and administration

The proposed dosage and administration of valemetostat was "the usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition." In addition, the "Precautions Concerning Dosage and Administration" section includes the following statements.

Precautions Concerning Dosage and Administration

- The efficacy and safety of valemetostat used in combination with other antineoplastic agents have not been established.
- Decreased C_{max} and AUC were reported with valemetostat administered after meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
- Criteria for dose adjustment in response to adverse drug reactions
- Dose of valemetostat when administered concomitantly with potent CYP3A inhibitor or P-gp inhibitor

As a result of the discussion in Sections "6.R.1 Timing of valemetostat administration," "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and inducers as well as P-gp inhibitors," "7.R.2 Efficacy," "7.R.3 Safety," and the following subsection, PMDA has concluded that the "Dosage and Administration" section should be as proposed, and the "Precautions Concerning Dosage and Administration" section should be specified as described below.

Precautions Concerning Dosage and Administration

- The efficacy and safety of valemetostat used in combination with other antineoplastic agents have not been established.
- Decreased C_{max} and AUC were reported with valemetostat administered after a meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
- When any adverse reaction of valemetostat occurs, valemetostat should be interrupted, reduced in dose, or discontinued according to the following criteria. The dose should not be reduced by >2 levels in response to the same adverse drug reaction.

Dose reduction levels of valemetostat

Level	Dose
Usual dose	200 mg
1-level reduced dose	150 mg
2-level reduced dose	100 mg
3-level reduced dose	50 mg
4-level reduced dose	Discontinuation

Criteria for dose adjustment of valemetostat

Adverse drug reaction	Severity	Measure
Neutrophil count decreased	Neutrophil count <500/mm^3 continued for >7 days	Interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Platelet count decreased	Platelet count <25,000/mm^3	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Anaemia	Hemoglobin value <8.0 g/dL, requiring red blood cell transfusion	Interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Non-hematotoxicity	Grade ≥3[Note)]	Interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.

Note) Graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

- Concomitant use of a potent CYP3A inhibitor or P-gp inhibitor may increase blood concentrations of valemetostat. The use of valemetostat should be considered with reference to the following criteria.

Criteria for dose adjustment of valemetostat when administered concomitantly with CYP3A inhibitor or P-gp inhibitor

Concomitant drug	Dose of valemetostat		
	200 mg	150 or 100 mg	50 mg
Potent CYP3A inhibitor	Reduce to 100 mg.	Reduce to 50 mg.	Do not use valemetostat concomitantly.
P-gp inhibitor			
Drug that potently inhibits CYP3A and P-gp	Reduce to 50 mg.	Do not use valemetostat concomitantly.	

7.R.5.1 Dosage and administration of valemetostat

The applicant's explanation about the dosage regimen of valemetostat:

In Study J201, the dosage regimen of valemetostat was specified as 200 mg orally administered in the fasted state QD because Study J101 indicated that this regimen would be recommended for patients with relapsed or refractory ATLL [see Section 7.1.3.1].

Study J201 conducted with the above dosage regimen demonstrated the clinical usefulness of valemetostat in patients with relapsed or refractory ATLL, and thus based on this regimen, the proposed dosage and administration of valemetostat were determined.

PMDA accepted the applicant's explanation.

7.R.5.2 Dose adjustment of valemetostat

The applicant's explanation about the dose adjustment of valemetostat in response to adverse drug reactions:

In Study J201, valemetostat was used in accordance with the pre-determined criteria for interruption, dose reduction, or discontinuation of valemetostat in response to adverse events and consequently tolerable, and thus the criteria for dose adjustment of valemetostat specified based on those in Study J201 were included in the "Precautions Concerning Dosage and Administration" section. In Study J201, the criteria for dose adjustment of valemetostat in response to Grade ≥3 electrocardiogram QTcF prolonged were specified in addition to those in response to non-hematotoxicity because mild QTc prolongation was observed in dogs receiving valemetostat in the 4-week repeated-dose toxicity study [see Section 3.2.2.2]. From results of Study J201 [see Section 7.R.3.5], however, a relationship of QT interval prolongation to valemetostat remains unclear at present, and thus the criteria for dose adjustment in response to electrocardiogram QTcF prolonged was not established.

PMDA's review:

PMDA accepted the above applicant's explanation and has concluded that the criteria for dose adjustment of valemetostat in response to adverse drug reactions should be modified as described below.

Precautions Concerning Dosage and Administration

- When any adverse drug reaction of valemetostat occurs, valemetostat should be interrupted, reduced in dose, or discontinued according to the following criteria. The dose should not be reduced by >2 levels in response to the same adverse drug reaction.

Dose reduction levels of valemetostat

Level	Dose
Usual dose	200 mg
1-level reduced dose	150 mg
2-level reduced dose	100 mg
3-level reduced dose	50 mg
4-level reduced dose	Discontinuation

Criteria for dose adjustment of valemetostat

Adverse drug reaction	Severity	Measure
Neutrophil count decreased	Neutrophil count <500/mm^3 continued for >7 days	Interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Platelet count decreased	Platelet count <25,000/mm^3	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Anaemia	Hemoglobin value <8.0 g/dL, requiring red blood cell transfusion	Interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Non-hematotoxicity	Grade ≥3[Note)]	Interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until recovers to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.

Note) Graded per NCI-CTCAE.

7.R.5.3 Concomitant use with the other antineoplastic agents

The applicant's explanation about concomitant use of valemetostat with the other antineoplastic agents in patients with relapsed or refractory ATLL:

At present, there are no data of clinical studies investigating the clinical usefulness of valemetostat concomitantly used with the other antineoplastic agents in patients with relapsed or refractory ATLL, and thus concomitant use of valemetostat with the other antineoplastic agents is not recommended for this patient population. Accordingly, the "Precautions Concerning Dosage and Administration" section notes that the efficacy and safety of valemetostat used in combination with the other antineoplastic agents have not been established.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:

In order to investigate the safety of valemetostat in post-marketing clinical use, the applicant planned to conduct post-marketing surveillance in all patients treated with valemetostat.

The safety specification in the surveillance is secondary malignant tumor, which is an event warranting special attention during the treatment with valemetostat, in view of incidences of adverse events in Study J201 and Study J101.

The planned sample size is 150 patients in view of the incidences of secondary malignant tumor in Studies J201 and J101.

The observation period is from the first dose of valemetostat to the end of the surveillance (6 years) in view of time to development of secondary malignant tumor in Study J101.

PMDA's review:
In light of the extremely limited safety information of valemetostat, the post-marketing surveillance should be conducted in all patients treated with valemetostat for a certain period after the market launch to collect the safety data promptly in an unbiased manner, and obtained safety information should be promptly provided to healthcare professionals.

The safety specification in the surveillance should be myelosuppression, infections, and secondary malignant tumor based on the review in Section "7.R.3 Safety."

The planned sample size and observation period for the surveillance should be reconsidered in view of incidences of the above events in clinical studies to be specified in the safety specification.

7.2 Adverse events, etc. observed in clinical studies

Deaths reported in the safety evaluation data were detailed in in Section "7.1 Evaluation data." The following subsection summarize major adverse events other than deaths.

7.2.1 Japanese phase I study (Study J103)

No adverse events occurred in Group 1 in Part 1 or 2.

In Group 2 in Part 2, adverse events occurred in 1 of 15 subjects (6.7%) after administration in the high-fat-meal fed state and 2 of 16 subjects (12.5%) after administration in the fasted state, and adverse events for which a causal relationship to valemetostat could not be ruled out occurred in 1 of 16 subjects (6.3%) after administration in the fasted state. Observed adverse events were ligament sprain in 1 subject (6.7%) after administration in the high-fat-meal fed state and blood fibrinogen increased, C-reactive protein increased, and contusion in 1 subject (6.3%) each after administration in the fasted state.

No serious adverse events occurred.

An adverse event leading to discontinuation of valemetostat occurred in 1 of 16 subjects (6.3%) after administration in the fasted state (none occurred after administration in the high-fat-meal fed state). Observed adverse events leading to discontinuation of valemetostat were blood fibrinogen increased and C-reactive protein increased in 1 subject (6.3%) each, and a causal relationship to valemetostat could not be ruled out for either event.

7.2.2 Japanese phase I study (Study J104)

7.2.2.1 Group 1

Adverse events occurred in 1 of 16 subjects (6.3%) in the valemetostat 25 mg alone group and 1 of 16 subjects (6.3%) in the valemetostat 25 mg plus itraconazole group, and there were no adverse events for which a causal relationship to the study drug could not be ruled out. Observed adverse events were upper respiratory tract infection in 1 subject (6.3%) in the valemetostat 25 mg alone group and upper respiratory tract infection in 1 subject (6.3%) in the valemetostat 25 mg plus itraconazole group.

There were neither serious adverse events nor adverse events leading to discontinuation of the study drug.

7.2.2.2 Group 2

Adverse events occurred in 7 of 16 subjects (43.8%) in the valemetostat 25 mg alone group and 1 of 13 subjects (7.7%) in the valemetostat 25 mg plus fluconazole group, and there were no adverse events for which a causal relationship to the study drug could not be ruled out. Observed adverse events were upper respiratory tract infection in 7 subjects (43.8%) in the valemetostat 25 mg alone group and upper respiratory tract infection in 1 subject (7.7%) in the valemetostat 25 mg plus fluconazole group.

No serious adverse events occurred.

Adverse events leading to discontinuation of the study drug occurred in 2 of 16 subjects (12.5%) in the valemetostat 25 mg alone group (none in the valemetostat 25 mg plus fluconazole group). Observed adverse events leading to discontinuation of the study drug were upper respiratory tract infection in 2 subjects (12.5%), and a causal relationship to the study drug was ruled out for both events.

7.2.3 Japanese phase I study (Study J107)

Adverse events occurred in 0 of 20 subjects in the valemetostat 200 mg alone group and 2 of 20 subjects (10.0%) in the valemetostat 200 mg plus rifampicin group, and an adverse event for which a causal relationship to the study drug could not be ruled out occurred in 1 of 20 subjects (5.0%) in the valemetostat 200 mg plus rifampicin group (none in the valemetostat 200 mg alone group). Observed adverse events were laryngeal pain, neutrophil count increased, and white blood cell count increased in 1 subject (5.0%) each in the valemetostat 200 mg plus rifampicin group (none in the valemetostat 200 mg alone group).

There were neither serious adverse events nor adverse events leading to discontinuation of the study drug.

7.2.4 Japanese phase I study (Study J109)

Adverse events occurred in 3 of 28 subjects (10.7%) after administration in the low-fat-meal fed state and 0 of 28 subjects after administration in the fasted state, and there were no adverse events for which a causal relationship to valemetostat could not be ruled out. Observed adverse events were

nasopharyngitis, diarrhoea, and ligament sprain in 1 subject (3.6%) each after administration in the low-fat-meal fed state (none occurred after administration in the fasted state).

There were neither serious adverse events nor adverse events leading to discontinuation of valemetostat.

7.2.5 Japanese phase II study (Study J201)

Adverse events occurred in 25 of 25 patients (100%), and adverse events for which a causal relationship to valemetostat could not be ruled out occurred in 24 of 25 patients (96.0%). Adverse events with an incidence of ≥20% were platelet count decreased in 20 patients (80.0%), anaemia in 12 patients (48.0%), alopecia in 10 patients (40.0%), dysgeusia in 9 patients (36.0%), neutrophil count decreased in 7 patients (28.0%), lymphocyte count decreased in 6 patients (24.0%), and decreased appetite, pyrexia, and white blood cell count decreased in 5 patients (20.0%) each.

Serious adverse events occurred in 8 of 25 patients (32.0%). Observed serious adverse events were cytomegalovirus chorioretinitis, cytomegalovirus infection reactivation, pneumonia, febrile neutropenia, cardiac failure, venous thrombosis limb, lower gastrointestinal haemorrhage, platelet count decreased, overdose, hepatic function abnormal, acute kidney injury, and hypercalcaemia in 1 patient (4.0%) each. A causal relationship to valemetostat could not be ruled out for cytomegalovirus chorioretinitis, cytomegalovirus infection reactivation, pneumonia, febrile neutropenia, cardiac failure, venous thrombosis limb, lower gastrointestinal haemorrhage, platelet count decreased, hepatic function abnormal, and acute kidney injury in 1 patient each.

Adverse events leading to discontinuation of valemetostat occurred in 2 of 25 patients (8.0%). Observed adverse events leading to discontinuation of valemetostat were cardiac failure and platelet count decreased in 1 patient (4.0%) each, and a causal relationship to valemetostat could not be ruled out for either event.

7.2.6 Global phase I study (Study J101)

7.2.6.1 Dose escalation part

Adverse events occurred in 7 of 7 patients (100%) in the valemetostat 150 mg cohort, 9 of 9 patients (100%) in the valemetostat 200 mg cohort, 7 of 7 patients (100%) in the valemetostat 250 mg cohort, and 2 of 2 patients (100%) in the valemetostat 300 mg cohort. Adverse events for which a causal relationship to valemetostat could not be ruled out occurred in 7 of 7 patients (100%) in the valemetostat 150 mg cohort, 9 of 9 patients (100%) in the valemetostat 200 mg cohort, 7 of 7 patients (100%) in the valemetostat 250 mg cohort, and 2 of 2 patients (100%) in the valemetostat 300 mg cohort. Adverse events with an incidence of ≥30% were platelet count decreased in 5 patients (71.4%), nasopharyngitis and dysgeusia in 4 patients (57.1%) each, anaemia, alopecia, and lymphocyte count decreased in 3 patients (42.9%) each in the valemetostat 150 mg cohort, platelet count decreased in 7 patients (77.8%), anaemia, dysgeusia, and ALT increased in 5 patients (55.6%) each, rash, neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, and aspartate aminotransferase (AST) increased in 4 patients (44.4%) each, nasopharyngitis, decreased appetite, and alopecia in 3 patients (33.3%) each in the valemetostat 200 mg cohort, platelet count decreased in 7 patients (100%), dysgeusia and lymphocyte count decreased in 6 patients (85.7%) each, alopecia and white blood cell

count decreased in 4 patients (57.1%) each, anaemia, diarrhoea, rash, and neutrophil count decreased in 3 patients (42.9%) each in the valemetostat 250 mg cohort, and anaemia, platelet count decreased, neutrophil count decreased, white blood cell count decreased, and lymphocyte count decreased in 2 patients (100%) each in the valemetostat 300 mg cohort.

Serious adverse events occurred in 3 of 7 patients (42.9%) in the valemetostat 150 mg cohort and 2 of 9 patients (22.2%) in the valemetostat 200 mg cohort (none in the valemetostat 250 mg and 300 mg cohorts). Observed serious adverse events were *Pneumocystis jirovecii* pneumonia, liver disorder, pancytopenia, and tumour lysis syndrome in 1 patient (14.3%) each in the valemetostat 150 mg cohort and tumour associated fever, liver disorder, and pyrexia in 1 patient (11.1%) each in the valemetostat 200 mg cohort. A causal relationship to valemetostat could not be ruled out for *Pneumocystis jirovecii* pneumonia in 1 patient in the valemetostat 150 mg cohort.

Adverse events leading to discontinuation of valemetostat occurred in 1 of 7 patients (14.3%) in the valemetostat 150 mg cohort (none in the valemetostat 200 mg, 250 mg, and 300 mg cohorts). An observed adverse event leading to discontinuation of valemetostat was *Pneumocystis jirovecii* pneumonia in 1 patient (14.3%) in the valemetostat 150 mg cohort, and the causal relationship to valemetostat could not be ruled out.

7.2.6.2 Dose expansion part

Adverse events occurred in 12 of 12 patients (100%) in the ATLL cohort and 40 of 40 patients (100%) in the PTCL cohort, and adverse events for which a causal relationship to valemetostat could not be ruled out occurred in 10 of 12 patients (83.3%) in the ATLL cohort and 32 of 40 patients (80.0%) in the PTCL cohort. Adverse events with an incidence of ≥20% were platelet count decreased in 8 patients (66.7%), dysgeusia in 6 patients (50.0%), alopecia and neutrophil count decreased in 5 patients (41.7%) each, anaemia, pruritus, dry skin, and arthralgia in 4 patients (33.3%) each, diarrhoea, white blood cell count decreased, ALT increased, and blood alkaline phosphatase (ALP) increased in 3 patients (25.0%) each in the ATLL cohort; and dysgeusia and platelet count decreased in 18 patients (45.0%) each, anaemia in 14 patients (35.0%), diarrhoea in 12 patients (30.0%), nausea, alopecia, and neutrophil count decreased in 11 patients (27.5%) each, white blood cell count decreased in 9 patients (22.5%), and cough in 8 patients (20.0%) in the PTCL cohort.

Serious adverse events occurred in 4 of 12 patients (33.3%) in the ATLL cohort and 14 of 40 patients (35.0%) in the PTCL cohort. Observed serious adverse events were cytomegalovirus infection, hypokalaemia, lactic acidosis, nervous system disorder, and urinary retention in 1 patient (8.3%) each in the ATLL cohort; and *Pneumocystis jirovecii* pneumonia, febrile neutropenia, and hypercalcaemia in 2 patient (5.0%) each and cytomegalovirus infection, cytomegalovirus chorioretinitis, epiglottitis, infection, tumour associated fever, coagulopathy, thrombocytopenia, hyperkalaemia, atrial fibrillation, cardiac failure acute, cardiomyopathy, pleural effusion, respiratory failure, acute kidney injury, and pyrexia in 1 patient (2.5%) each in the PTCL cohort. A causal relationship to valemetostat could not be ruled out for cytomegalovirus infection and urinary retention in 1 patient each in the ATLL cohort and *Pneumocystis jirovecii* pneumonia in 2 patients and cytomegalovirus infection, infection, and febrile neutropenia in 1 patient each in the PTCL cohort.

An adverse event leading to discontinuation of valemetostat occurred in 1 of 40 patients (2.5%) in the PTCL cohort (none in the ATLL cohort). An observed adverse event leading to discontinuation of valemetostat was colitis in 1 patient (2.5%) in the PTCL cohort, and the causal relationship to valemetostat could not be ruled out.

7.2.7 Foreign phase I study (Study U105)

Adverse events occurred in 4 of 8 subjects (50.0%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 1 of 8 subjects (12.5%). An adverse event with an incidence of ≥20% was diarrhoea in 2 subjects (25.0%).

There were neither serious adverse events nor adverse events leading to discontinuation of the study drug.

7.2.8 Foreign phase I study (Study U106)

An adverse event occurred in 1 of 24 subjects (4.2%), and there were no adverse events for which a causal relationship to valemetostat could not be ruled out. An observed adverse event was toothache in 1 subject (4.2%).

There were neither serious adverse events nor adverse events leading to discontinuation of valemetostat.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is currently ongoing, and the results and the conclusion of PMDA will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The assessment is currently ongoing, and the results and the conclusion of PMDA will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that valemetostat has efficacy in the treatment of relapsed or refractory ATLL, and that valemetostat has acceptable safety in view of its benefits. Valemetostat is a drug with a new active ingredient expected to suppress tumor growth by inhibiting methylation of EZH1/2 and thereby inducing apoptosis. Thus valemetostat is of clinical significance as a treatment option for relapsed or refractory ATLL. The clinical positioning, indication, dosage and administration, etc. are subject to further review.

PMDA has concluded that valemetostat may be approved if valemetostat is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 4, 2022

Product Submitted for Approval

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of the discussion in Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of valemetostat had been demonstrated to a certain degree in patients with relapsed or refractory ATLL in the Japanese phase II study (Study J201) targeted this patient population by the primary endpoint, i.e., the centrally-assessed response rate [95% CI] (%) of 48.0 [27.8, 68.7] (12 of 25 patients) according to the modified version of criteria proposed by the International Conference on Human Retrovirology, meeting the pre-determined efficacy criteria.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the discussion in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that adverse events requiring special attention during the treatment with valemetostat are myelosuppression, infections, and secondary malignant tumor.

PMDA concluded that, valemetostat is tolerable in patients with relapsed or refractory ATLL, albeit the above-mentioned adverse events that warrant attention during the treatment, as long as physicians with adequate knowledge and experience in treatment of hematopoietic malignancy take appropriate measures, such as monitoring and controlling of adverse events, and dose interruption, reduction, or discontinuation of valemetostat.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

As a result of the discussion in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that the indication of valemetostat should be defined as "relapsed or refractory adult T-cell leukemia-lymphoma" as proposed, while offering information such as disease types and the status of unfavorable prognostic factors of patients enrolled in Study J201 in the "Clinical Studies" section of the package insert, along with the following advice in the "Precautions Concerning Indication" section .

Precautions Concerning Indication

- Physicians should be well-versed in the information presented in the "Clinical Studies" section, including the disease types of the patients enrolled in the clinical studies and the presence or absence of poor prognostic factors in these patients, and have full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration

As a result of the discussion in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that the Dosage and Administration and Precautions Concerning Dosage and Administration section of valemetostat should be described as below.

Dosage and Administration

The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of valemetostat used in combination with the other antineoplastic agents have not been established.
- Decreased C_{max} and AUC were reported with valemetostat administered after meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
- When any adverse reaction of valemetostat occurs, valemetostat should be interrupted, reduced in dose, or discontinued according to the following criteria. The dose should not be reduced by >2 levels in response to the same adverse drug reaction.

Dose reduction levels of valemetostat

Level	Dose
Usual dose	200 mg
1-level reduced dose	150 mg
2-level reduced dose	100 mg
3-level reduced dose	50 mg
4-level reduced dose	Discontinuation

Criteria for dose adjustment of valemetostat

Adverse drug reaction	Severity	Measure
Neutrophil count decreased	Neutrophil count <500/mm^3 continued for >7 days	Interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Platelet count decreased	Platelet count <25,000/mm^3	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Anaemia	Hemoglobin value <8.0 g/dL, requiring red blood cell transfusion	Interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Non-hematotoxicity	Grade ≥3[Note)]	Interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.

Note) Graded per NCI-CTCAE.

- Concomitant use of a potent CYP3A inhibitor or P-gp inhibitor may increase blood concentrations of valemetostat. The use of valemetostat should be considered with reference to the following criteria.

Criteria for dose adjustment of valemetostat when administered concomitantly with CYP3A inhibitor or P-gp inhibitor

Concomitant drug	Dose of valemetostat		
	200 mg	150 or 100 mg	50 mg
Potent CYP3A inhibitor	Reduce to 100 mg.	Reduce to 50 mg.	Do not use valemetostat concomitantly.
P-gp inhibitor			
Drug that potently inhibits CYP3A and P-gp	Reduce to 50 mg.	Do not use valemetostat concomitantly.	

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to specify the Dosage and Administration and Precautions Concerning Dosage and Administration section as described above. The applicant agreed.

1.5 Risk management plan (draft)

In order to investigate the safety of valemetostat in its post-marketing clinical use, the applicant plans to conduct a post-marketing surveillance in all patients treated with valemetostat. The planned sample size is 150 patients and the observation period will begin with the first dose of valemetostat and last until the end of the surveillance (6 years).

As a result of the discussion in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA concluded that the post-marketing surveillance should be conducted covering all patients treated with valemetostat for a certain period after the market launch to collect safety information in prompt

and unbiased manners, and the obtained safety information should be offered immediately to healthcare professionals.

PMDA further concluded on the surveillance plan that:
- The safety specification of the surveillance should include myelosuppression, infections, and secondary malignant tumor.
- The planned sample size and observation period for the surveillance should be reconsidered in view of the occurrence of those events of safety specification in the clinical studies.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above review, PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:
- The safety specification of the surveillance will include myelosuppression, infections, and secondary malignant tumor.
- The planned sample size for the surveillance is 150 in view of the incidences of the events of safety specification in the clinical studies.
- The observation period for the surveillance is 1 year for myelosuppression and infections, and 3 years for secondary malignant tumor in view of the timing of onset of these events in the clinical studies.

PMDA accepted the applicant's response.

Based on the discussion above, PMDA has concluded that the risk management plan (draft) for valemetostat should include the safety specification presented in Table 28, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 29 and 30.

Table 28. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Myelosuppression • Infections • Drug interactions with CYP3A inhibitors and P-gp inhibitors	• Secondary malignant tumor • Reproductive and developmental toxicity	Not applicable
Efficacy specification		
Not applicable		

Table 29. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (all-case surveillance)	Not applicable	• Information provision based on the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

Table 30. Outline of use-results survey (draft)

Objective	To investigate safety of valemetostat in post-marketing settings
Survey method	All-case surveillance
Population	All patients treated with valemetostat
Observation period	1 year (for secondary malignant tumor, 3 years after the first dose of valemetostat)
Planned sample size	150
Main survey items	Safety specification: Myelosuppression, infections, and secondary malignant tumor Other main survey items: Patient characteristics (age, sex, disease type, medical history, complications, etc.), prior treatment, use status of valemetostat, concomitant drugs, adverse events, etc.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration defined below with the following approval conditions, only when it is assured that the package insert offers appropriate cautionary advice, information about proper use is delivered appropriately in the post-marketing setting; and valemetostat is properly used by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy at medical institutions capable of emergency response. The product is designated as an orphan drug, and the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Relapsed or refractory adult T-cell leukemia-lymphoma

Dosage and Administration

The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Given the extremely limited number of Japanese patients participated in clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data are gathered from a certain number of patients to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Warnings

The product should be administered only when patients are found to be eligible for the treatment with the product by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancy, and at medical institutions capable of emergency response. Prior to treatment, the benefits and risks of the treatment should be thoroughly explained to the patient or their family, and consent should be obtained.

Contraindication

Patients with a history of hypersensitivity to any ingredient of the product

Precautions Concerning Indication

Physicians should be well-versed in the information presented in the "Clinical Studies" section, including the disease types of the patients enrolled in the clinical studies and the presence or absence of poor prognostic factors in these patients, and have full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of valemetostat used in combination with other antineoplastic agents have not been established.
2. Decreased C_{max} and AUC were reported with valemetostat administered after meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
3. When any adverse drug reaction of valemetostat occurs, valemetostat should be interrupted, reduced in dose, or discontinued according to the following criteria. The dose should not be reduced by >2 levels in response to the same adverse drug reaction.

Dose reduction levels of valemetostat

Level	Dose
Usual dose	200 mg
1-level reduced dose	150 mg
2-level reduced dose	100 mg
3-level reduced dose	50 mg
4-level reduced dose	Discontinuation

Criteria for dose adjustment of valemetostat

Adverse drug reaction	Severity	Measure
Neutrophil count decreased	Neutrophil count <500/mm^3 continued for >7 days	Interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Platelet count decreased	Platelet count <25,000/mm^3	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Anaemia	Hemoglobin value <8.0 g/dL, requiring red blood cell transfusion	Interrupt valemetostat until the hemoglobin value recovered to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.
Non-hematotoxicity	Grade ≥3[Note)]	Interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at one-level lower dose than the previous dose.

Note) Graded the NCI-CTCAE.

4. Concomitant use of a potent CYP3A inhibitor or P-gp inhibitor may increase blood concentrations of valemetostat. The use of valemetostat should be considered with reference to the following criteria.

Criteria for dose adjustment of valemetostat when administered concomitantly with CYP3A inhibitor or P-gp inhibitor

<table>
<tr><th rowspan="2">Concomitant drug</th><th colspan="3">Dose of valemetostat</th></tr>
<tr><th>200 mg</th><th>150 or 100 mg</th><th>50 mg</th></tr>
<tr><td>Potent CYP3A inhibitor</td><td rowspan="2">Reduce to 100 mg.</td><td rowspan="2">Reduce to 50 mg.</td><td rowspan="3">Do not use valemetostat concomitantly.</td></tr>
<tr><td>P-gp inhibitor</td></tr>
<tr><td>Drug that potently inhibits CYP3A and P-gp</td><td>Reduce to 50 mg.</td><td>Do not use valemetostat concomitantly.</td></tr>
</table>

List of Abbreviations

AEBP2	AE binding protein 2
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
Application	application for marketing approval
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATLL	adult T-cell leukemia-lymphoma
BCRP	breast cancer resistance protein
BID	bis in die
BUN	blood urea nitrogen
CCR4	CC chemokine receptor 4
CD	cluster of differentiation
CHL cell line	Chinese hamster lung cell line
CI	confidence interval
CL_r	renal clearance
CMV	cytomegalovirus
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CRu	complete response unconfirmed
CYP	cytochrome P450
^{14}C-valemetostat	^{14}C-labeled valemetostat tosilate
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DN	CD4 and CD8 double negative
DP	CD4 and CD8 double posit
ECOG	Eastern Cooperative Oncology Group
EED	embryonic ectoderm development
efflux ratio	ratio of secretion permeability coefficient in the secretive direction to that in the absorptive direction
EZH	enhancer of zeste homolog
EZH1/2	enhancer of zeste homolog 1 and 2
F1	bioavailability
FRET	fluorescence resonance energy transfer
GC	gas chromatography
GGT	gamma-glutamyltransferase
HBc antibody	anti-hepatitis B core antigen
HBs antigen	hepatitis B surface antigen
HBs antibody	anti-hepatitis B surface antigen
HBV	hepatitis B virus
HDAC	histone deacetylase
hERG	human *ether-a-go-go*-related gene
H3K27	histone H3 lysin 27
HLT	high level term
HMT	histone metyltransferase
HPLC	high performance liquid chromatography
Ht	hematocrit
HTLV-1	human T-cell leukemia virus type 1

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E guideline	“Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ILD	interstitial lung disease
IR	infrared absorption spectroscopy
K_i	inhibition constant
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LDH	lactate dehydrogenase
Lenalidomide	Lenalidomide hydrate
LOCI	Luminescent oxygen channeling immunoassay
MATE	multidrug and toxin extrusion
M/E	myeloid/erythroid
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	multiple myeloma
Mogamulizumab	Mogamulizumab (genetical recombination)
MPE	mean photo effect
mRNA	messenger ribonucleic acid
mSWAT	modified Severity Weighted Assessment Tool
MTD	maximum tolerated dose
NA	not assessable
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in T-Cell Lymphomas
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NF-κB	nuclear factor κ B
NHL	non-Hodgkin lymphoma
NK cells	natural killer cell
NMR	nuclear magnetic resonance spectroscopy
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
PAG1	phosphoprotein associated with glycosphingolipid-enriched microdomains 1
P_{app}	apparent permeability
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PEG	polyethylene glycol
P-gp	P-glycoprotein
PIF	photo irritation factor
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PRC2	polycomb-repressive complex 2
PS	performance status
PT	preferred term
PTCL	peripheral T-cell lymphoma
QD	quaque die

QTcF	QT interval corrected by Fridericia method
ΔQTcF	Change from baseline in QTcF
RBBP4	retinoblastoma binding protein 4
RD	Relapse disease
SCID mouse	severe combined immunodeficient mouse
SD	stable disease
SLA	src-like adaptor protein
SMQ	standard MedDRA queries
SOC	system organ class
Study J101	Study DS3201-A-J101
Study J103	Study DS3201-A-J103
Study J104	Study DS3201-A-J104
Study J107	Study DS3201-A-J107
Study J109	Study DS3201-A-J109
Study J201	Study DS3201-A-J201
Study U105	Study DS3201-A-U105
Study U106	Study DS3201-A-U106
SUZ12	suppressor of zeste 12
TCR	T cell receptor
Treg	regulatory T cells
UV-A	ultraviolet light-A
UV/VIS	ultraviolet-visible spectroscopy
Valemetostat	Valemetostat Tosilate
V/F	apparent volume of distribution
VZV	varicella zoster virus